Stereoselective deprotonation of tropinone and reactions of tropinone lithium enolate

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Tropinone (**6**) was deprotonated with lithium diisopropylamide and with chiral lithium amides (**18–24**) and the resulting enolates (two enantiomers) were treated with electrophiles. The aldol reaction with benzaldehyde and deuteration were both diastereoselective. The former yielded only one isomer (*exo*, *anti*) of the aldol **8***a*; the latter proceeded from the *exo* face. This selectivity permitted us to probe the deprotonation of tropinone with lithium amides; it was concluded that the reaction involves predominantly the *exo* axial protons. The reaction of tropinone enolate with ethyl chloroformate led, via a ring opening, to the cycloheptenone derivative **9**. The reaction with methyl cyanoformate yielded, in the presence of silver acetate and acetic acid, the β-ketoester **8***b*; however, in the absence of these additives, and especially when 12-crown-4 was added to the enolate, a ring opening leading to the pyrrolidine derivative **10** occurred instead. Deprotonation of tropinone with chiral lithium amides proceeded with modest enantioselectivity. A synthesis of non-racemic anhydroecgonine via this strategy allowed establishing the absolute stereochemistry of deprotonation.

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On a déprotoné la tropinone (**6**) à l'aide du diisopropylamidure de sodium et des amidures de lithium chiraux (**18–24**) et l'on a traité les énolates qui se sont formés (deux énantiomères) avec des électrophiles. La réaction aldolique avec le benzaldéhyde ainsi que la deutération sont toutes les deux diastéréosélectives; la première ne fournit qu'un isomère (*exo*, *anti*) de l'aldol **8***a* alors que la dernière se produit par la face *exo*. Cette sélectivité a permis d'examiner la déprotonation de la tropinone avec des amidures de lithium; on en a conclu que la réaction implique principalement les protons axiaux *exo*. La réaction de l'énolate de tropinone avec le chloroformate d'éthyle conduit, par le biais d'une ouverture de cycle, au dérivé cyclohepténone **9**. La réaction avec le cyanoformate de méthyle, réalisée en présence d'acétate d'argent et d'acide acétique, conduit au β-cétoester **8***b*; toutefois, lorsque cette addition est réalisée en l'absence de ces additifs et particulièrement lorsqu'on ajoute de l'éther 12-couronne-4 à l'énolate, il se produit plutôt une ouverture de cycle conduisant au dérivé de la pyrrolidine **10**. La déprotonation de la tropinone sous l'influence d'amidures de lithium se produit avec une énantiosélectivité modeste. Une synthèse de l'anhydroecgonine non-racémique à l'aide de cette stratégie a permis d'établir la stéréochimie absolue de la déprotonation.

[Traduit par la rédaction]

Introduction

Reactions that differentiate efficiently between two enantiotopic groups are often encountered in bioorganic chemistry when enzymes are used as reagents (1). In more classical synthetic organic chemistry such reactions are rare (2). Indeed the scarcity of group-enantioselective reactions has led some researchers to caution against complications of synthetic problems arising from symmetry in starting materials (3). Development of methods for achieving enantiotopic group selectivity is thus important; one such method that emerged recently as a promising new synthetic tool involves enantioselective deprotonation of ketones (4). The method is shown in general terms in Scheme 1; an achiral (or *meso*) ketone **1**, which has an internal plane of symmetry and thus belongs to the C_s point group, reacts with a chiral lithium amide **2** to yield a non-racemic mixture of lithium enolates (**3s**, **r**) which further react with an electrophile to give a number of products (**4**, **5**; only one enantiomer of each of these compounds is shown in Scheme 1). The goal is to achieve control over reaction selectivity, i.e., one of the products should predominate.

In this paper we describe our studies on the deprotonation of tropinone (**6**) (5); apart from theoretical interest in studying the scope and limitations of enantioselective deprotonation, we hoped that deprotonation of this *meso* ketone, followed by reactions of the resulting enolates with electrophiles, might lead to the development of a synthetic strategy suitable for the construction of a number of tropane alkaloids (6) in a stereoselective manner.

Results and discussion

A metal enolate of tropinone has three electron-rich centers that could be attacked by an electrophile: the α-carbon, the oxygen, and the nitrogen; depending on the character of the electrophile either one of these centers can participate in the reaction (*vide infra*).

Deprotonation of tropinone with LDA

Relatively little is known about generation and reactions of tropinone lithium enolates (6); for that reason, and also to find a suitable method of determination of the enantiomeric excess of tropinone deprotonation, we first investigated reactions of this ketone with lithium diisopropylamide (LDA) followed by electrophilic attack (Scheme 2). The racemic mixture of tropinone lithium enolates, generated by mixing tropinone with LDA in THF at −78°C, was treated with a number of electrophiles. The results are summarized in Table 1 (the differences between yields presented in Table 1 and these in ref. 5*a* reflect the changes in experimental procedures made since preliminary results of this work were published).

Chlorotrimethylsilane (entry 1) and acetic anhydride (entry 2) yielded the racemic mixtures of the O-silylated and O-acetylated products **7***a* (E = $SiMe_3$) and **7***b* (E = COMe), respectively. In the first case the quality of chlorotrimethylsilane proved crucial. Use of a chlorotrimethylsilane–triethylamine mixture, from which the amine hydrochloride was removed by centrifugation, a common procedure in silyla-

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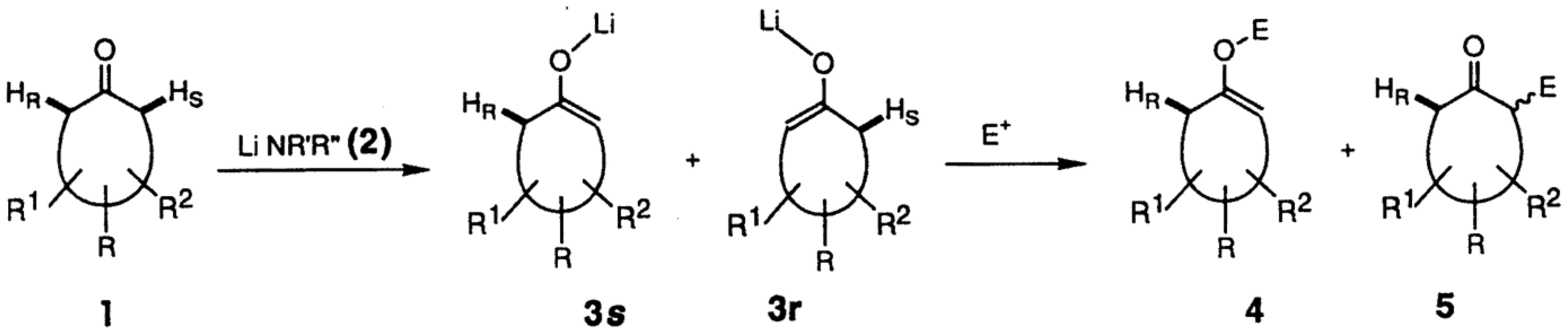
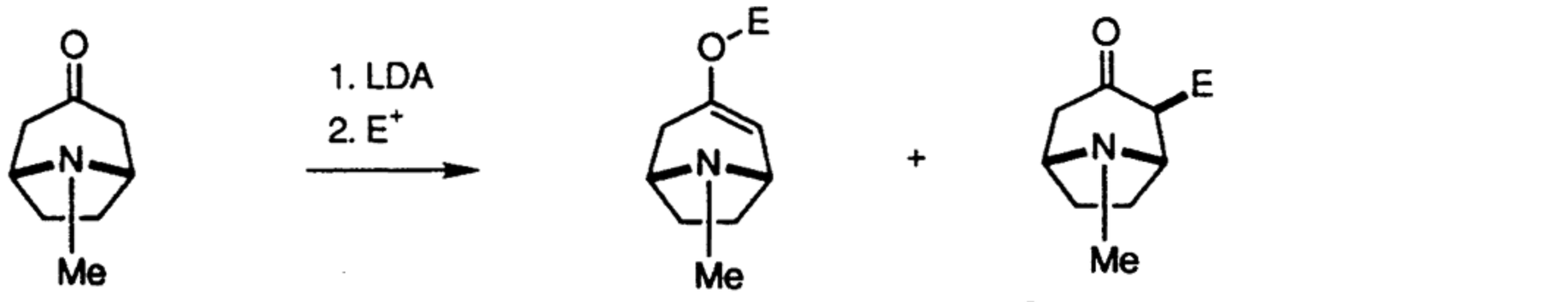


SCHEME 1



SCHEME 2

TABLE 1. Reactions of tropinone lithium enolate with electrophiles.

Entry	E^+	Product	Yield (%)[a]
1	Me_3SiCl	**7***a*	88
2	Ac_2O	**7***b*	54
3	PhCHO	**8***a*	88
4	Cl-COOEt	**9**	87
5	CN-COOMe	**8***b*	82
6	PhCOCl	**8***c*	62
7	DEAD	**8***d*	80
8	D_2O	**8***e*	81

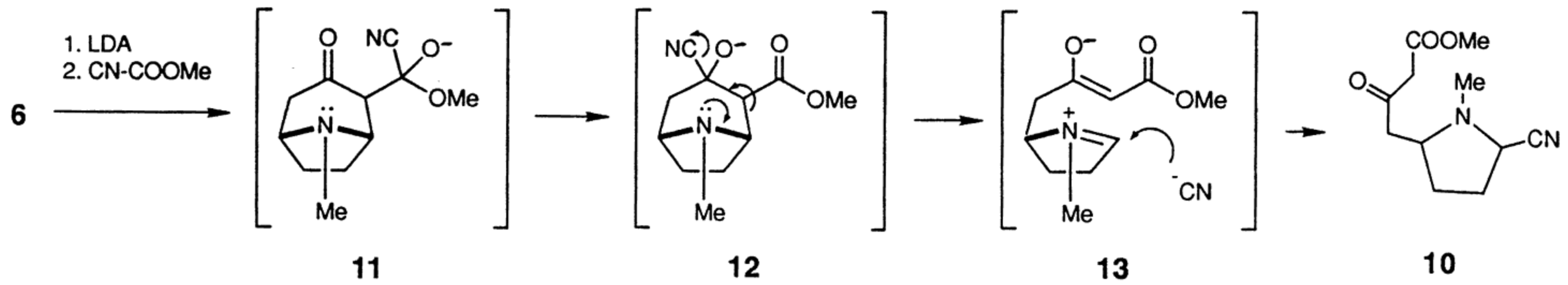
[a]Yields refer to isolated, pure products.

tion reactions, led to low yields both when Corey's internal quench (7) and the normal procedure of quenching the preformed enolate with one equivalent of chlorosilane were tried. This was, conceivably, due to triethylamine hydrochloride protonating the enolate. Good yield was achieved by purifying TMSCl by distillation from CaH_2 followed by storage over polyvinylpyridine (Reillex 402) (8), and using the internal quench procedure.

Benzaldehyde (entry 3), methyl cyanoformate (entry 5), benzoyl chloride (entry 6), and diethylazodicarboxylate (DEAD; entry 7) reacted at the carbon terminus. Interestingly, the reaction with benzaldehyde was highly stereoselective and gave only one diastereoisomer out of a possible four. Lithium enolates of cyclic ketones are known to give predominantly *anti* aldols (9); the vicinal coupling constant J_{AB} in the ^1H NMR of the aldol product **8***a* was, however, only 3 Hz, which suggested the *syn* configuration (9*a*). In agreement with both steric and stereoelectronic effects we expected this product to be the *exo* isomer; the *exo* face of tropinone should be less hindered sterically in analogy to norbornyl ring systems (10*a*). Alkylation of endocyclic six-membered enolates is known to proceed predominantly from the axial direction, which, in systems where steric constrains are absent, was rationalized by stereoelectronic effects (10, 11). We finally determined that the aldol **8***a* was indeed the *exo-anti* isomer by NMR studies on a cyclic derivative (5*a*) and by X-ray analysis of compound **8***a*, which fortunately was crystalline.[2] The low J_{AB} value is probably due to the fact that, in solution, the OH group of **8***a* is hydrogen-bonded to the nitrogen (similar hydrogen bonding is pseudotropine was reported before) (12).

To gain an entry into alkaloids related to cocaine we wanted to attach an ester synthon to the tropinone ring. Towards this end we treated the racemic mixture of tropinone lithium enolates with ethyl chloroformate, a reagent that was

[2]The X-ray data will be published elsewhere.



SCHEME 3

often used for carboethoxylation (13). Unexpectedly this led to formation of cycloheptenone **9** via ring opening.[3] Chloroformates are known to demethylate tropinone and other tertiary amines (14) but the reaction leading to **9** is clearly of a different type; it can be viewed as an electrophilic attack on nitrogen in tandem with E1cB elimination.

The reaction with chloroformate was thus unsuccessful as far as making of the β-ketoester was concerned. We next turned our attention to methyl cyanoformate, developed by Mander and co-workers as a reagent for α-carbomethoxylation of ketones (15*a*). Initially, reaction of tropinone lithium enolate with this reagent produced the desired β-ketoester **8***b*, which exists as a mixture of keto and enol forms, in low yield (45%). The major by-product isolated from this reaction was the substituted pyrrolidine **10** (Scheme 3, relative stereochemistry unknown). After a brief study of the reaction conditions we found that when, prior to addition of the cyanoformate reagent, one equivalent of 12-crown-4 was added to the enolate, the pyrrolidine derivative **10** became the major product (74% isolated yield) and only a small amount of the β-ketoester **8***b* was formed. When one equivalent of LiBr was added to the enolate, however, the amount of pyrrolidine **10** was much smaller and the yield of **8***b* increased to 70%. We rationalized these observations as follows:

Mander and Crabtree observed formation of ketone cyanohydrins of β-ketoesters in reactions of ketone enolates with cyanoformate (15). It seems, therefore, reasonable to envisage that intermediate **12** (Scheme 3) plays an important role in the reaction. This intermediate presumably undergoes Grob fragmentation (16), which leads to the undesired pyrrolidine **10**; to minimize this side reaction the formation of **12** has to be suppressed. The experiment with LiBr, addition of which increased the yield of the β-ketoester **8***b*, indicated that a Lewis acid retarded the Grob pathway; we attributed this to the LiBr complexation with the CN ion, which attenuated the nucleophilicity of this anion. In an effort to further decrease the ability of CN^- to attack the C=O, acetic acid was added to the reaction mixture instead of LiBr. The acid was expected to convert the cyanide to the less nucleophilic HCN: we subsequently added silver acetate to trap HCN as silver cyanide. This strategy worked; the desired β-ketoester **8***b* was now produced in 94% yield (82% after column chromatography).

Deuteration of tropinone lithium enolate with D_2O, using a second equivalent of *n*-BuLi to prevent "internal return" of the proton according to the procedure developed by Seebach and co-workers (17), showed the same face selectivity as the aldol reaction and yielded only one monodeuterated product **8***e*, the *exo* isomer. This allowed us to address the question: is the deprotonation of tropinone diastereoselective? Due to steric and stereoelectronic effects (*vide supra*) the axial *exo* protons should undergo abstraction faster than the equatorial ones.

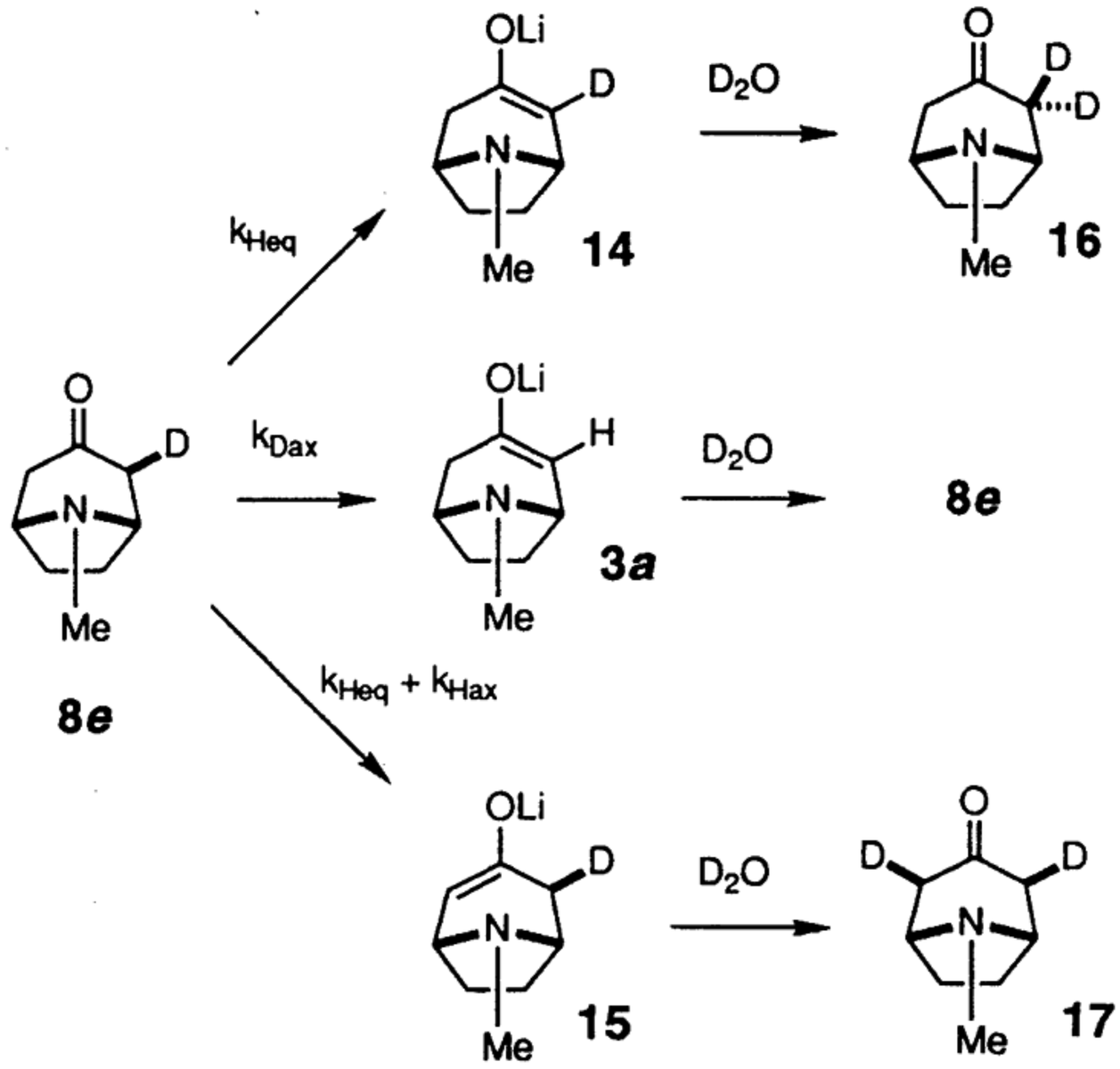
Both ^1H and ^{13}C NMR spectra of tropinone were described before (18), however, there is some confusion in the literature concerning proton assignments (cf. difference in assignments in ref. 18*a* and ref. 18*b*). Since we intended to use NMR for the analysis of deuterated tropinones, we reinvestigated the proton NMR spectrum using nuclear Overhauser effects to help identify all the protons. The proton assignments and nOe's are shown in Fig. 1. It should be noted that the six-membered ring of tropinone is known to assume the chair conformation with the methyl group being equatorial (18).

Only one product (**8***e*) was isolated from lithiation of tropinone with LDA, followed by addition of one equivalent of *n*-BuLi and deuteration with D_2O (17). This product was the *exo* isomer, as evidenced by the 50% decrease in the intensity of the NMR signal at 2.69 ppm (the signal at 2.20 ppm remained unchanged). The *exo* **8***e* was then subjected to another deprotonation with LDA followed by treatment of the enolate with *n*-BuLi and then by quenching with D_2O. We envisaged that, if the base removed any of the equatorial protons, producing enolates **14** and (or) **15**, we should find the geminal bis-deuterotropinone **16** in the products (Scheme 4). The formation of the isomer **17**, with both deuterium atoms axial, could result from either axial or equatorial deprotonation. We did not detect compound **16** either by ^1H or by ^{13}C NMR which led us to the conclusion that the deprotonation of tropinone with LDA is highly diastereoselective: the axial (*exo*) protons are removed at least 12 times faster than the equatorial (*endo*) protons (assuming that deprotonation is not reversible and that NMR provides 5% detection level of **16**; if 5% of **16** was indeed produced this would indicate the relative rate of proton abstraction k_{Hax}/k_{Heq} of 12–17 depending on the magnitude of the primary deuterium isotope effect).

Deprotonation with chiral lithium amides

Abstraction of an α-proton from tropinone (**6**) with a chiral lithium amide (**18–24**), followed by quenching of the resulting non-racemic mixture of tropinone lithium enolates with benzaldehyde, yielded two enantiomers of the aldol product **8***a*. The enantiomeric excess (ee) was determined by NMR; when the ^1H and ^{13}C spectra of samples of **8***a* were taken in the presence of optically active shift reagent

[3]We later learned that this ring-opening reaction had also been observed by Simpkins, who reported it in a lecture, cf. ref. 4*b*.



SCHEME 4

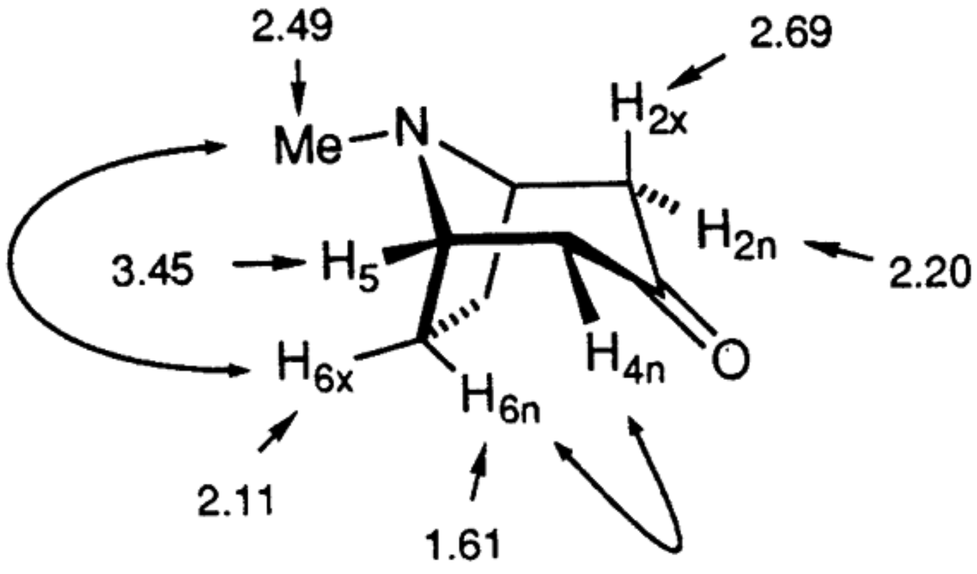


FIG. 1. Proton chemical shifts and nOe's (double-headed arrows) of tropinone (**6**).

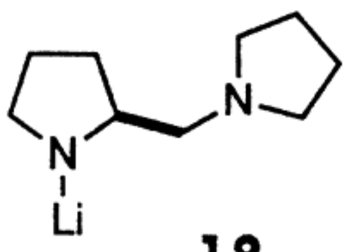
(+)-Eu(tfc)$_3$, the splitting of the singlet corresponding to the N-Me group was observed. When the racemic **8***a*, obtained using LDA as the base, was analysed by this method the ratio of the peaks in the N-Me singlet split in the presence of Eu(tfc)$_3$ was 52:48, which provided some measure of the accuracy of this technique. The results of our enantioselective deprotonation experiments are shown in Table 2. The observed selectivities were modest with an optimum ee of 60%. We were able, however, to obtain an optically pure sample of compound **8***a* by fractional crystallization (19).

In an effort to improve enantioselectivity we investigated the effect of reaction conditions (bases **22** and **23** were used in this brief study). Lowering the reaction temperature to −100°C, as well as using two equivalents of base or an additional equivalent of *n*-BuLi, had no effect on enantioselectivity. Use of HMPA or sparteine as additives decreased the ee by up to three quarters (i.e., 10% ee instead 40% when base **23** was used in the presence of sparteine).

To establish the absolute stereochemistry of the proton abstraction with chiral lithium amides and also to highlight the potential practical utility of the method we synthesised non-racemic anhydroecgonine methyl ester (**27**), a natural product of known configuration (20*b*), via this enantioselective deprotonation strategy. The synthesis is shown in Scheme 5. A non-racemic sample of compound **8***b* was obtained in 95% yield according to the method described above (deprotonation of tropinone with base **22** followed by treatment with methyl cyanoformate, AcOH, and AcOAg). Due to tautomerism, compound **8***b* exists as a mixture of isomers with, presumably, the carboxymethyl group disposed equatorially in the major isomer. The keto group in **8***b* was reduced with sodium borohydride. It was found that under standard conditions ($NaBH_4$ in EtOH) only a small amount of **8***b* underwent reduction. However, upon lowering the reaction temperature to −60°C and addition of a small amount of aqueous NH_4Cl the reduction proceeded well (presumably due to the change in the keto–enol equilibrium of the starting material) and yielded a mixture of two products **25** and **26** in a ratio of 6:1 (80% yield). Compounds **25** and **26** were separated[4] and were then subjected to dehydration. It was found that compound **25** (but not **26**) underwent a facile dehydration with trifluoroacetic anhydride – triethylamine. Compound **26** (but not **25**) was easily dehydrated with triflic anhydride – triphenylphosphine oxide. Elimination of trifluoroacetate esters with Et_3N presumably proceeds via the E2 mechanism, hence compound **26**, in which the hydrogen atom and the OH group are *cis*, could not be easily dehydrated with the $(CF_3CO)_2O$–Et_3N mixture. The method utilizing triphenylphosphine and trifluoromethylsulfonic anhydride, developed by Hendrickson and Hussoin (21), presumably involves *syn* elimination. This would account for the easy dehydration of compound **26** under these conditions.

[4]The relative configurations of these compounds were assigned on the basis of the comparison of their NMR spectra with the spectra of cocaine and its isomers reported by Carroll *et al.*; cf. ref. 20*c*.

TABLE 2. Enantioselective deprotonation of tropinone with bases **18–24** followed by aldol addition



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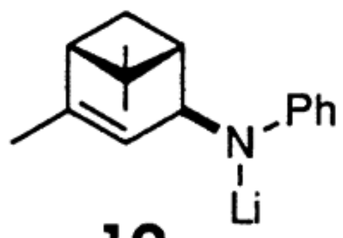

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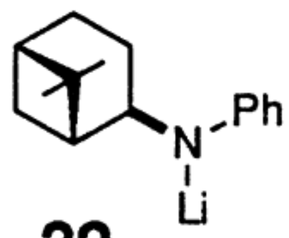

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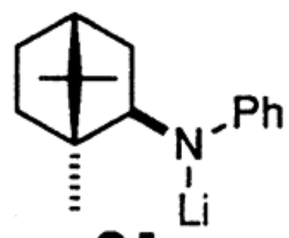

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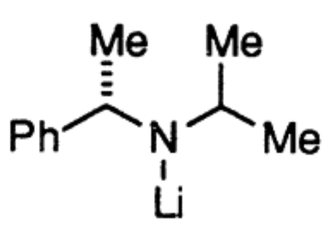

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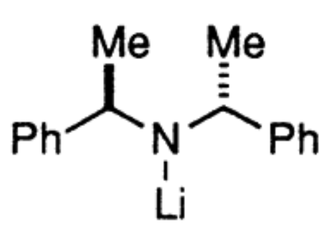

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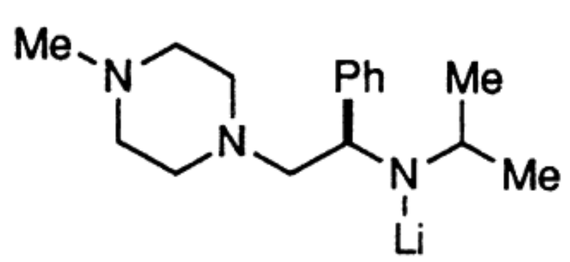

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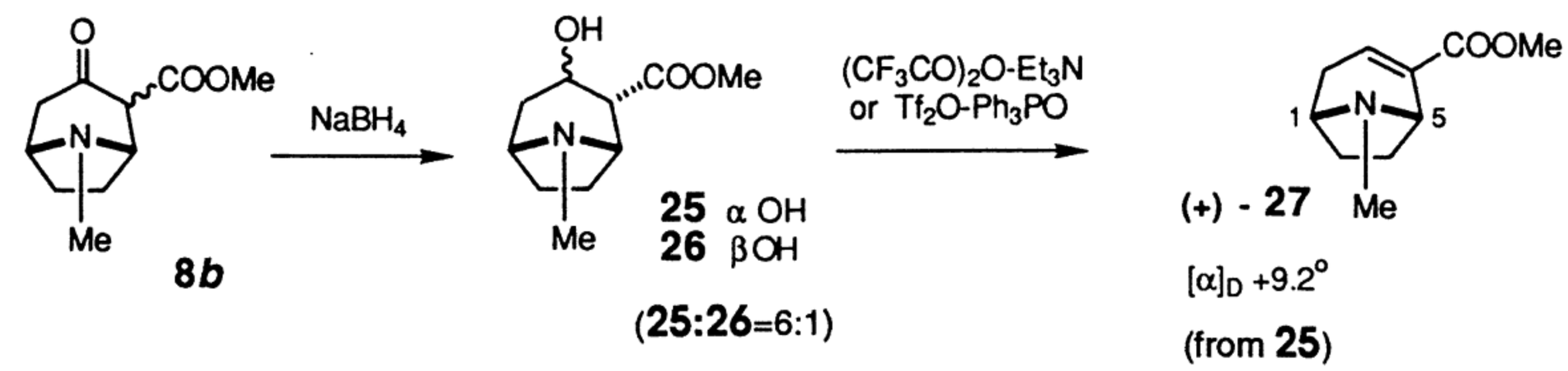
Entry	Base[a]	Yield (%)[b]	ee (%)[b]	Isomer[b,c]
1	**18**	85	8	(+)-2*R*
2	**19**	97	16	(−)-2*S*
3	**20**	70[d]	26	(−)-2*S*
4	**21**	75[d]	40	(−)-2*S*
5	**22**	88	34	(+)-2*R*
6	**23**	84	40	(−)-2*S*
7	**24**	64	60	(+)-2*R*

[a]Optically pure bases **18–24** were used (cf. Experimental).
[b]Yields and ee refer to compound **8***a*.
[c]The absolute stereochemistry was established by correlating the structure of **8***a* with that of ecgonine Me ester.
[d]A small amount (less than 5%) of the *endo-anti* isomer of **8***a* was observed.



SCHEME 5

The optically active **27** was thus obtained, via the sequence described above, in 71% yield from an achiral starting material (tropinone) and had the optical rotation of +9.2. Since the optically pure levorotatory anhydroecgonine methyl ester, derived from cocaine, was reported (20*a*) to have $[\alpha]_D^{20}$ of −43, the optical purity of our sample was calculated to be 21% (the optical purity of compound **27** could not be measured by NMR as no separation of peaks due to enantiomers in the presence of optically active shift reagents was observed).

The absolute configuration of levorotatory anhydroecgonine methyl ester is known (6, 20); this isomer has the carbomethoxy group at C-2 (Scheme 5; tropane alkaloid numbering). This allowed us to determine the absolute stereochemistry of proton abstraction: bases **18**, **22**, and **24** remove preferentially the pro-*S* proton of tropinone (from C-4) and bases **19–21** and **23** deprotonate faster at C-2 (pro-*R* axial hydrogen); this was in agreement with the results of Simpkins (4*b*).

In conclusion, we have established that: (*i*) deprotonation of tropinone with LDA is diastereoselective and involves the axial (*exo*) protons. (*ii*) The aldol addition of tropinone Li enolate is also diastereoselective and produces the *exo-anti* aldol. (*iii*) Chloroformates react with the Li-enolate of tropinone to give a product of ring opening (**9**). (*iv*) Tropinone can be deprotonated enantioselectively with chiral lithium amides. Although the optical yields observed so far were modest, we are pursuing the potential use of this strategy in the stereoselective synthesis of tropane alkaloids. The strategy was highlighted by a short synthesis of non-racemic anhydroecgonine methyl ester (**27**).

Experimental

All moisture-sensitive reactions were carried out under argon. THF was distilled from a dark-blue solution containing sodium benzophenone ketyl under nitrogen atmosphere. Diisopropylamine, triethylamine, pyridine, DMF, TMEDA, and dichloromethane were distilled from calcium hydride under nitrogen atmosphere, and then stored in 100-mL Sure-seal™ bottles containing 4Å molecular sieves under argon. TMSCl was twice dis-

tilled from calcium hydride under argon atmosphere, and then stored in a 100-mL Sure-seal™ bottle with Reillex™ 402 (8). Acetic anhydride was distilled from calcium carbide (22), then redistilled before storing over 4Å molecular sieves under argon. Benzoyl chloride was stirred with oven-dried calcium carbonate powder for 2 days; the filtered liquid was then dried over sodium sulfate. After distillation, the purified benzoyl chloride was stored with 4Å molecular sieves under argon. Benzaldehyde was washed with 10% aqueous calcium carbonate solution and dried over calcium chloride prior to fractional distillation (22). Butyllithium was titrated periodically using 2,5-dimethoxybenzyl alcohol as indicator. Lithum bromide was flame-dried under vacuum and stored in a sealed flask under an argon atmosphere; it was used as a stock solution in THF (~3 M). Flash column chromatographic separations were performed with Merck Kieselgel 60 (230–400 mesh ASTM). All thin-layer chromatography (TLC) was carried out using precoated glass plates with Silica Gel 60 F254. The spots were detected by using UV light, or phosphomolybdic acid/$Ce(SO_4)_2$ solution followed by charring on a hot plate.

Melting points are uncorrected. Gas chromatography was performed using a Hewlett Packard 5890A with a HP-1 column (methyl silica gum, 5 m × 0.53 mm × 2.65 mm film thickness). The CHN elemental analyses were done using a Perkin Elmer 2400 CHN elemental analyzer. Low-resolution mass spectra were obtained using a VG Analytical retro-fitted MS-12. All NMR spectra were recorded on a Brucker AM 300 (^{1}H at 300 MHz; ^{13}C at 75 MHz) using $CDCl_3$ as solvent and TMS (tetramethylsilane) as internal standard (δ_{TMS} = 0.00 ppm).

*3-Trimethylsiloxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (7*a)

TMSCl (5.5 mmol; 0.7 mL) was added to a solution of LDA (1.1 mmol) in THF (3.2 mL) followed by the dropwise addition of a solution of tropinone (1.0 mmol; 0.139 g) in THF (2 mL) over 15 min at −78°C. After 5 min the mixture was quenched with triethylamine (1.5 mL) and was then warmed to room temperature; the remaining TMSCl, triethylamine, and THF were removed on a rotary evaporator. The pure product (185 mg, 88%) was obtained after distillation from Kugelrohr apparatus: bp 218°C; IR (KBr) 3045, 2958, 2937, 2844, 2794, 1651, 1251, 893, 845 cm^{-1}; ^{1}H NMR δ: 4.92 (d, J = 5.6 Hz, 1H), 3.28 (d, J = 5.3 Hz, 1H), 3.26 (d, J = 5.7 Hz, 1H), 2.53 (dd, J_1 = 20.0 Hz, J_2 = 9.7 Hz, 1H), 2.37 (s, 3H), 2.13 (m, 1H), 2.00 (m, 1H), 1.83 (m, 1H), 1.58 (m, 2H), 0.20 (s, 9H); ^{13}C NMR δ: 147.1 (OC), 106.5 (CH), 57.9 (CH), 57.2 (CH), 35.7 (NCH_3), 35.3 (CH_2), 34.9 (CH_2), 29.8 (CH_2), 0.1 ($SiCH_3$); MS (CI–NH_3) m/z: 214 (8.3), 213 (25.3), 212 (100.0), 211 (9.1), 183 (18.8), 182 (37.8). Anal. calcd. for $C_{11}H_{21}NOSi$: C 62.50, H 10.01, N 6.63; found: C 62.40, H 10.22, N 6.81.

General procedure for generation of tropinone lithium enolate and its reaction with electrophiles

Diisopropylamine (0.155 mL; 1.1 mmol) was dissolved in THF (3.2 mL), and cooled to 0°C. *n*-Butyllithium (1.1 mmol; 0.48 mL of a 2.3 M solution in hexane) was added to the solution. The resulting, colourless, solution of LDA was stirred for 25 min at 0°C and was then cooled to −78°C. Tropinone **6** (0.139 g; 1.0 mmol), dissolved in THF (2 mL), was added dropwise over 15 min to the solution. The resulting mixture was stirred for 45 min at −78°C and was then treated with an appropriate electrophile. After the reaction mixture was stirred for a specified period of time the reaction was quenched with saturated aqueous NH_4Cl solution at −78°C. The reaction mixture was then allowed to warm to room temperature and was extracted with CH_3Cl (3 × 10 mL). The combined organic layers were washed with water, then dried over sodium sulfate, and the solvents were removed on a rotary evaporator to give the crude product.

*3-Acetoxy-8-methyl-8-azabicyclo[3.2.1]oct-2-ene (7*b)

Acetic anhydride (5.3 mmol; 0.5 mL) was added to a solution of tropinone lithium enolate (1.0 mmol) in THF (3.2 mL) and the mixture was stirred at −78°C for 1 h. After the standard work-up, the crude product **7***b* was obtained as a yellow oil (117 mg; 64%). Purification by chromatography (SiO_2; 5% MeOH in CH_3Cl) and bulb-to-bulb distillation (50°C/0.5 Torr; 1 Torr = 133.3 Pa) afforded **7***b* as a colourless oil (97 mg, 54%). IR (KBr) 2939, 2798, 1757, 1676, 1432, 1212, 1116 cm^{-1}; ^{1}H NMR δ: 5.46 (dd, J_1 = 1.3, J_2 = 4.2 Hz, 1H), 3.37 (m, 2H), 2.67 (dd, J_1 = 3.7 Hz, J_2 = 17.1 Hz, 1H), 2.44 (s, 3H), 2.18 (m, 1H), 2.11 (s, 3H), 2.05 (m, 1H), 1.91 (dt, J_1 = 8.9 Hz, J_2 = 2.5 Hz, 1H), 1.71 (d, J = 17.0 Hz, 1H), 1.66 (m, 1H); ^{13}C NMR δ: 169.1 (CO), 145.1 (OC), 116.4 (CH), 57.9 (CH), 57.2 (CH), 35.3 (NCH_3), 34.6 (CH_2), 29.9 (CH_2), 21.0 (CH_3); MS (EI) m/z: 183 (0.3), 182 (3.4), 181 (19.4), 138 (19.3), 111 (27.5), 110 (100.0), 96 (27.3).

*(1*R**, 2*S**, 1'*R**)-2-(1'-Hydroxybenzyl)-8-methyl-8-azabicyclo[3.2.1]octan-3-one (8*a)

The general procedure was followed with PhCHO as electrophile. The reaction mixture was stirred at −78°C for 15 min. After standard work-up, a yellowish solid was obtained (216 mg; 88%).

The crude product was dissolved in a minimum amount of chloroform in a warm water bath. Hexane was then added dropwise until the solution became cloudy. A small amount of $CHCl_3$ was added until the mixture became clear again. The clear solution was cooled down slowly to room temperature, and white needles of the racemate were collected (183 mg, 75%); m.p. 132.7°C; IR (KBr) 3399, 3086, 2954, 2880, 2807, 1711, 1491, 1452, 1077, 760, 701 cm^{-1}; ^{1}H NMR δ: 7.19–7.40 (m, 5H), 5.21 (d, J = 3.1 Hz, 1H), 3.57 (d, J = 6.6 Hz, 1H), 3.43–3.48 (m, 1H), 2.84 (ddd, J_1 = 15.6 Hz, J_2 = 4.6 Hz, J_3 = 1.5 Hz, 1H), 2.44 (s, 3H), 2.39–2.42 (m, 1H), 2.30 (ddd, J_1 = 15.7 Hz, J_2 = 2.0 Hz, J_3 = 2.0 Hz, 1H), 2.07–2.25 (m, 2H), 1.44–1.65 (m, 2H); ^{13}C NMR δ: 208.0 (CO), 141.7 (C), 128.0 (CH), 127.3 (CH), 125.2 (CH), 76.5 (CHOH), 67.1 (CHN), 63.8 (CHN), 61.5 (CH), 51.6 (CH_2), 40.5 (CH_3N), 26.3 (CH_2), 26.1 (CH_2); MS (CI, NH_3) m/z: 247 (17.7), 246 (100.0), 140 (51.9), 82 (20.1). Anal. calcd. for $C_{15}H_{19}NO_2$: C 73.44, H 7.81, N 5.71; found: C 73.50, H 8.06, N 5.70.

The ee was measured by ^{1}H NMR. Small amounts of (+)-Eu(tfc)$_3$ were added to the sample in $CDCl_3$ solution until a sufficient separation of the peak corresponding to the N-Me group (originally at 2.44 ppm) was achieved.

*(+)-(1*S*, 2*R*, 1'*S*)-2-(1'-Hydroxybenzyl)-8-methyl-8-azabicyclo[3.2.1]octan-3-one (8*a)

A solution of tropinone (1.0 mmol; 0.139 g) in THF (2 mL) was added dropwise over 15 min, to the preformed yellowish solution of lithium amide **22** (1.1 mmol) in THF (3.2 mL) and the mixture was stirred for 45 min at −78°C. Benzaldehyde (1.2 mmol; 0.127 mL) in THF (1 mL) was added to the reaction mixture at −78°C and, after 15 min, the reaction was quenched with saturated NH_4Cl solution (2 mL). After standard work-up, the crude mixture was placed under high vacuum for 2 days. A yellow solid was obtained (212 mg; 86% yield).

Optical purity of the crude **8***a* was 34% as measured by ^{1}H NMR using (+)-Eu(tfc)$_3$. The compound was recrystallized from $CHCl_3$–hexane as described above. White needles of the racemate were collected first and the solvent from the mother liquid was removed, and the remaining solid was again subjected to recrystallization. After repeating this procedure several times, an enantiometrically pure product was obtained as yellow rhombic crystals: mp 132–133°C; $[\alpha]_D^{20}$ + 23 (c 0.0173 g/mL, $CHCl_3$).

*Methyl 8-methyl-3-oxo-8-azabicyclo[3.2.1]octane-2-carboxylate (8*b*) (ref. 20*b*)*

Methyl cyanoformate (1.3 mmol; 0.1 mL) was added dropwise to a solution of tropinone lithium enolate (1.0 mmol) in THF (3.2 mL) at −78°C. The mixture was stirred at −78°C for 20 min. Glacial acetic acid (1 mL), and then silver acetate (1 mmol; 0.168 g) in glacial acetic acid (1 mL) were added to the mixture at −78°C. The mixture was warmed to room temperature, stirred for 30 min, and concentrated NH_4OH solution was added until the

mixture became clear. The resulting solution was extracted with $CHCl_3$ (5 × 30 mL), the combined organic extracts were washed with water, dried (Na_2SO_4), and the solvent was removed to give an off-white solid (187 mg; 95% yield).

Purification by flash chromatography (SiO_2, 5% MeOH in $CHCl_3$) yielded a white solid that was a mixture of keto and enol forms of **8***b* (161 mg, 82%): IR (KBr): 2951, 2851, 2799, 1741, 1718, 1652, 1615, 1443, 1227, 813 cm^{-1}; ^1H NMR δ: 3.78 (m, 1H), 3.76 (s, 64% 3H), 3.74 (s, 36% 3H), 3.37–3.66 (1H), 3.12–3.37 (1H), 2.67–2.93 (1H), 2.53 (s, 13% 3H), 2.38 (s, 22% 3H), 2.36 (s, 65% 3H), 2.03–2.32 (3H), 1.74–1.94 (1H), 1.48–1.66 (1H); MS (CI, isobutane) *m/z*: 198 (100), 166 (23). Anal. calcd. for $C_{10}H_{15}NO_3$: C 60.89, H 7.67, N 7.10; found: C 60.59, H 7.72, N 6.98.

*2-Benzoyl-8-methyl-8-azabicyclo[3.2.1]oct-2-en-3-ol (**8**c)*

The general procedure was followed with benzoyl chloride (2.6 mmol; 0.3 mL, 2.5 equivalents) as the electrophile. The mixture was stirred at −78°C for 30 min, before saturated NH_4Cl solution (2 mL) was added to the reaction mixture. Na_2CO_3 solution (40%) was added to the resulting yellow mixture until pH ~9. Extraction, followed by column chromatography (SiO_2, 5% MeOH in $CHCl_3$), yielded a yellow solid of **8***c* (150 mg; 62%); mp 75.2–77.2°C; IR (KBr) 3058, 2945, 2849, 2796, 1716, 1678, 1595, 1568, 1447, 1400, 1273, 1146, 697 cm^{-1}; ^1H NMR δ: 7.43–7.57 (m, 5H), 3.82 (d, J = 6.0 Hz, 1H), 3.41 (t, J = 6.1 Hz, 1H), 2.91 (ddd, J_1 = 19.3 Hz, J_2 = 5.5 Hz, J_3 = 1.9 Hz, 1H), 2.28–2.42 (m, 1H), 2.32 (s, 3H), 2.22 (t, J = 9.5 Hz, 2H), 2.02 (m, 1H), 1.70 (m, 1H); ^{13}C NMR δ: 195.6 (CO), 181.2 (OC=C), 135.6 (C), 130.6 (CH), 128.3 (CH), 128.1 (CH), 112.8 (C=C), 59.6 (CH), 58.0 (CH), 40.4 (CH_2), 37.1 (NCH_3), 33.9 (CH_2), 29.2 (CH_2); MS (El) *m/z*: 245 (0.7), 244 (5.4), 243 (21.2), 215 (54.1), 214 (100.0), 136 (20.6), 110 (12.2), 105 (39.5), 82 (52.8). Anal. calcd. for $C_{15}H_{17}NO_2$: C 74.05, H 7.04, N 5.76; found: C 73.83, H 6.82, N 5.51.

*2-(1, 2-Dicarbethoxyhydrazo)-8-methyl-8-azabicyclo[3.2.1]-octan-3-one (**8**d)*

DEAD (1.9 mmol; 0.3 mL) was added to a solution of tropinone lithium enolate (1.0 mmol) in THF (3.2 mL) and the mixture was stirred at −78°C for 30 min. After standard work-up the yellowish, oily product **8***d* was obtained (295 mg, 94%). The product was purified by flash chromatography (SiO_2; 5% MeOH in $CHCl_3$). The purified product **8***d* was a yellow solid (250 mg, 80%): mp 81.2–82.2°C; IR (KBr) 3295, 3252, 2978, 2957, 2883, 2766, 1746, 1712, 1508, 1468, 1302, 1231, 1095 cm^{-1}; ^1H NMR δ: 6.81–7.09 (br, 1H), 4.99–5.21 (br, 1H), 4.13 (q, J = 7.0 Hz, 4H), 3.58–3.68 (br, 1H), 3.41 (br, 1H), 2.69 (d, J = 15.1 Hz, 1H), 2.52 (br, 3H), 2.23 (d, J = 15.3 Hz, 1H), 1.80–2.12 (br, 3H), 1.49 (m, 1H), 1.19 (two overlap. t, J = 7.0 Hz, 6H); ^{13}C NMR δ: 205.4 (CO), 204.9 (CO), 156.6 (COO), 156.0 (COO), 65.1 (CH), 64.8 (CH), 62.8 (OCH_2), 61.8 (OCH_2), 61.3 (CH), 61.0 (CH), 46.7 (CH_2), 46.4 (CH_2), 38.5 (CH), 37.4 (CH_3), 37.2 (CH_3), 27.9 (CH_2), 27.5 (CH_2), 24.5 (CH_2), 24.2 (CH_2), 14.4 (CH_3), 14.3 (CH_3); MS (CI (NH_3)) *m/z*: 316 (2.6), 315 (17.5), 314 (100.0), 313 (12.3), 225 (20.3), 85 (20.2), 83 (31.2), 82 (37.2). Anal. calcd. for $C_{14}H_{23}N_3O_5$: C 53.66, H 7.40, N 13.41; found: C 53.57, H 7.58, N 13.58.

*(exo)-2-Deutero-8-methyl-8-azabicyclo[3.2.1]octan-3-one (**8**e)*

n-Butyllithium (2.2 mmol; 1.05 mL of 2.1 molar solution in hexane), was added dropwise to a solution of tropinone lithium enolate (2.0 mmol) in THF (5.2 mL) at −78°C, and the mixture was then warmed to 0°C for 20 min. The reaction mixture was then cooled down to −78°C, D_2O (5 mL, 99% D) was added, and the mixture was warmed first to 0°C for 3 min, then to room temperature. Extraction and removal of the solvents using first a rotary evaporator and then high vacuum gave a greenish solid.

Pentane was added to the crude solid dropwise at 40°C until all the solid had dissolved. The solution was then cooled down to −30°C for several hours. The solvent was removed from the crystals at this low temperature via a syringe, and the crystals of the pure **8***e* were washed with cold pentane. Yield: 227 mg; 81%; mp 40.5–42.0°C; IR (KBr): 3387, 2934, 2882, 2855, 2802, 1714, 1592, 1476, 1348 cm^{-1}; ^1H NMR δ: 3.44 (br, 2H), 2.69 (dd, J_1 = 4.0 Hz, J_2 = 16.0 Hz, 1H), 2.49 (s, 3H), 2.20 (d, J = 15.3 Hz, 2H), 2.11 (m, 2H), 1.61 (m, 2H); ^{13}C NMR δ: 211.1 (CO), 60.7 (CH), 47.6 (CH_2), 47.3 (t, J = 18.2 Hz, CHD), 38.3 (CH_3), 27.6 (CH_2); MS (CI (NH_3)) *m/z*: 144 (18.0), 143 (20.3), 142 (69.8), 141 (100.0), 140 (84.2), 138 (17.0), 83 (91.9).

*(exo, exo)-2,4-Dideutero-8-methyl-8-azabicyclo[3.2.1]octan-3-one (**17**)*

2-Deuterotropinone (**8***e*) (1.0 mmol; 140 mg) in THF (1.2 mL) solution was added dropwise to a solution of LDA (1.1 mmol) in THF (3.2 mL) at −78°C. After 40 min, *n*-BuLi (1.1 mmol; 0.52 mL of 2.1 molar solution in hexane) was added slowly to the mixture at −78°C. The mixture was then warmed to 0°C for 20 min and cooled down to −78°C again. D_2O (5 mL, 99%D) was added to the reaction mixture at −78°C, and then warmed to 0°C for 3 min, then to room temperature. Extraction and removal of solvents by rotary evaporator, followed by high vacuum, gave a greenish solid (141 mg; 100%). The solid was purified by crystallization from pentane as described above. Yield: 110 mg (78%), mp 42–43°C; IR (KBr): 2932, 2882, 2856, 2802, 2216, 1702, 1475, 1344, 1146, 483, 453 cm^{-1}; ^1H NMR δ: 3.45 (br, 2H), 2.70 (dd, J_1 = 3.9 Hz, J_2 = 16.0 Hz, 33% of 2H), 2.50 (s, 3H), 2.20 (d, J = 15.4 Hz, 2H), 2.12 (m, 2H), 1.61 (m, 2H); ^{13}C NMR δ: 211.1 (CO), 60.7 (CH), 47.6 (CH_2), 47.3 (t, J = 18.2 Hz, CHD), 38.3 (CH_3), 27.6 (CH_2); MS (CI − NH_3) *m/z*: 145 (8.4), 144 (46.2), 143 (83.4), 142 (100.0), 141 (69.8), 140 (29.3).

*6-(N-Carbethoxy-N-methyl)aminocyclohept-2-en-1-one (**9**)*

Ethyl chloroformate (4.7 mmol; 0.45 mL) was added slowly to a solution of tropinone lithium enolate (1.0 mmol) in THF (3.2 mL) and stirred for 10 min at −78°C. Saturated NH_4Cl solution (2 mL) was added at −78°C, the mixture was warmed to room temperature, and 40% Na_2CO_3 solution (3 mL) was added to make the mixture basic. The organic layer was separated, and the aqueous layer was extracted with chloroform (4 × 5 mL). After drying (Na_2SO_4) and removal of the solvent from the combined organic layers the product was purified by chromatography (SiO_2, 4:1 hexane:AcOEt). Yellow oil (184 mg; 87%), bp 275°C; IR (KBr): 3022, 2978, 2936, 2872, 1693, 1667, 1483, 1405, 1314, 1155, 772 cm^{-1}; ^1H NMR δ: 6.64 (ddd, J_1 = 11.5 Hz, J_2 = 6.3 Hz, J_3 = 4.6 Hz, 1H), 6.04 (d, J = 12.1 Hz, 1H), 4.60 (br, 1H), 4.14 (q, J = 7.1 Hz, 2H), 2.84 (m, 2H), 2.80 (s, 3H), 2.42–2.68 (m, 2H), 1.87–2.14 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ: 14.4 (OCH_2CH_3), 29.0 (CH), 30.4 (CH_2), 47.8 (CH_2), 50.9 (NCH_3), 61.0 (OCH_2CH_3), 132.2 (CH), 146.2 (CH), 155.6 (NCOO), 200.3 (CO); MS (EI, 20eV) *m/z*: 211 (60), 138 (66), 108 (95), 104 (100). Anal. calcd. for $C_{11}H_{17}NO_3$: C 62.54, H 8.11, N 6.63; found: C 62.70, H 8.38; N 6.76.

*Methyl 4-[2'-(5'-cyano-1'-methylpyrrolidinyl)]-3-oxo-butyrate (**10**)*

12-Crown-4 (1.1 mmol; 0.194 g) in THF (1 mL) was added to a solution of tropinone lithium enolate (1.0 mmol) in THF (3.2 mL) at −78°C. The mixture was warmed to 0°C for 10 min, and was then cooled to −78°C. Methyl cyanoformate (1.3 mmol; 0.1 mL) was added and the reaction mixture was stirred for 30 min at −78°C. After the standard work-up, and the removal of solvents, the crude product was purified by chromatography (SiO_2, 1:1 hexane:AcOEt), yielding a white solid (165 mg; 74%). Mp 78.8–79.8°C; IR (KBr): 2954, 2855, 2799, 2242, 1745, 1715, 1630, 1565, 1437, 1323, 1258, 1198, 1161, 1048 cm^{-1}; ^1H NMR δ: 3.93 (d, J = 6.7 Hz, 1H), 3.75 (s, 3H), 3.48 (s, 2H), 2.98 (m, 1H), 2.87 (dd, J_1 = 17.0 Hz, J_2 = 3.8 Hz, 1H), 2.58 (q, J = 8.5 Hz, 1H), 2.43 (s, 3H), 2.34 (m, 1H), 2.02–2.18 (m, 2H), 1.58 (m, 1H); ^{13}C NMR δ: 201.0 (CO), 167.4 (COO), 117.3 (CN), 58.3 (OCH3), 56.5 (CH), 52.4 (CH), 49.6 (CH_2), 47.0 (CH_2), 36.6 (NCH_3), 29.2 (CH_2), 28.0 (CH_2); MS (CI, NH_3) *m/z*: 227 (1.4), 226 (13.0), 225 (97.3), 224 (2.0), 198 (39.7), 109 (100.0), 82

(24.4), 225 (46.0), 198 (100.0), 109 (19.0), 82 (12.0). Anal. calcd. for $C_{11}H_{16}N_2O_3$: C 58.91, H 7.19, C 12.49; found: C 58.76, H 7.12, C 12.71.

*Methyl (*endo, endo*)-3-hydroxy-8-methyl-8-azabicycyclo[3.2.1]-octane-2-carboxylate (**25**) and methyl (2-*endo, *3-*exo*)-3-hydroxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylate (**26**)*

Compound **8***b* (1.0 mmol; 0.197 g) was dissolved in absolute ethanol (2.5 mL) at room temperature, and the solution was then cooled down to −60°C. Sodium borohydride (5.3 mmol; 0.200 g) was added to the clear solution. A small amount of solid NH_4Cl was then added to the mixture followed by addition of saturated NH_4Cl solution (0.5 mL). The reaction mixture was stirred at −60°C for 3 h, was then allowed to warm to room temperature, and stirred overnight. The excess of $NaBH_4$ was destroyed by adding acetic acid (glacial) dropwise. The solvent and excess AcOH were removed on a rotary evaporator, and the residue was dissolved in $CHCl_3$ (10 mL). Na_2CO_3 (40% solution, 5 mL) was added and the mixture was then extracted with $CHCl_3$ (4 × 15 mL). After washing with water, the combined organic layers were dried (Na_2SO_4). The solvent was removed and the crude product was dried under high vacuum, yielding an oily solid (159 mg; 80%). ^{1}H NMR showed that the product contained 86% of **25** and 14% of **26**.

These two isomers were separated by flash chromatography (SiO_2, 5% MeOH in $CHCl_3$); **26** (20 mg; 10%) was eluted first followed by **25** (133 mg; 67%).

Compound **25**: IR (neat): 3700–3100, 1740 cm^{-1}; ^{1}H NMR δ: 4.28 (t, J = 4.5 Hz, 1H), 3.76 (s, 3H), 3.49 (br, 1H), 3.23 (br, 1H, OH), 3.17 (br, 1H), 3.00 (t, J = 3.5 Hz, 1H), 2.32 (s, 3H), 1.94–2.16 (m, 5H), 1.82 (m, 1H); ^{13}C NMR δ: 24.2 (CH_2), 25.8 (CH_2), 38.7 (CH_2), 40.0 (CH), 50.0 (CH), 52.0 (CH), 60.3 (NCH_3), 62.1 (CH), 64.9 (OCH_3), 173.9 (CO); MS (EI) m/z: 199 (15), 97 (58), 96 (78), 83 (58), 82 (100). Anal. calcd. for $C_{10}H_{17}NO_3$: C 60.28, H 8.60, N 7.03; found: C 60.05, H 8.67, N 6.78.

Compound **26**: IR (neat): 3700–3100, 1740 cm^{-1}; ^{1}H NMR δ: 4.12 (dt, J_1 = 10.3 Hz, J_2 = 6.6 Hz, 1H), 3.74 (s, 3H), 3.48 (dd, J_1 = 6.1 Hz, J_2 = 2.6 Hz, 1H), 3.24 (m, 1H), 2.72 (dd, J_1 = 9.9 Hz, J_2 = 2.9 Hz, 1H), 2.38 (s, 3H), 1.68–2.08 (m, 4H), 1.54 (q, J = 8.6 Hz, 2H); ^{13}C NMR δ: 25.0 (CH_2), 27.2 (CH_2), 36.1 (CH_2), 38.0 (CH), 52.1 (CH), 52.2 (CH), 60.1 (NCH_3), 62.0 (CH), 64.8 (OCH_3), 175.0 (CO); MS (Cl (NH_3)) m/z: 201 (12.3), 200 (100), 83 (24). Anal. calcd. for $C_{10}H_{17}NO_3$: C 60.28, H 8.60, N 7.03; found: C 60.17, H 8.90, N 6.78.

*Anhydroecgonine methyl ester (**27**) (ref. 20*a*)*

(*a*) (±)-(**27**): Triphenylphosphine oxide (0.4 mmol; 0.111 g) was dissolved in anhydrous dichloromethane (0.5 mL) and placed in a septum-sealed 10-mL round-bottom flask at 0°C, under argon. Trifluoromethanesulfonic anhydride (0.2 mmol; 34 mL) in anhydrous dichloromethane (0.5 mL) was added dropwise to the reaction mixture with constant stirring. The reddish colour of triphenylphosphine oxide solution disappeared immediately after the triflic anhydride had been added. Racemic compound **26** (0.1 mmol; 20 mg) in dry dichloromethane (0.5 mL) was added slowly at 0°C, and the reaction mixture was then warmed to room temperature and stirred for 15 min. Anhydrous triethylamine (0.5 mL) was added to the reaction mixture and the reddish color appeared again. After 15 min, the reaction was quenched with water (2 mL), and then extracted with diethyl ether (5 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate. After removal of the solvent, the residue was subjected to separation on a short column (SiO_2, 3% MeOH in $CHCl_3$), which yielded the purified product (15 mg; 83%).

(*b*) (+)-(**27**): Non-racemic **25** (5.5 mmol; 1.1 g), was prepared as previously described using chiral base **22**, and dissolved in anhydrous dichloromethane (4 mL) in a septum-sealed 10-mL round-bottom flask at 0°C, under argon. Anhydrous triethylamine (15.8 mmol; 2.2 mL) was added, followed by a catalytic amount of 4-(dimethylamino)pyridine in dichloromethane (1.2 mL) solution. The solution was stirred and trifluoroacetic anhydride (7.1 mmol, 1.0 mL) in dichloromethane (2.5 mL) was added dropwise during 20 min. After stirring for an additional 2 h at 0°C, the reaction mixture was warmed to room temperature and stirred for another 30 h. The reaction mixture was then cooled down to 0°C again, and treated with dilute Na_2CO_3 solution until the solution became basic. The mixture was extracted with chloroform (5 × 30 mL), and the combined organic layers were washed (H_2O), and then dried (Na_2SO_4). After removal of the solvent, the mixture was subjected to flash chromatography (SiO_2, 3% MeOH in $CHCl_3$). A colorless oil was obtained (925 mg; 93%): $[\alpha]_D^{20}$ + 9.2 (*c* 0.1084 g/mL, MeOH), IR (KBr): 2949, 2876, 2843, 2793, 1711, 1639, 1436, 1253, 1084, 753, 728 cm^{-1}; ^{1}H NMR δ: 1.52 (m, 1H), 1.85 (t, J = 9.8 Hz, 1H), 1.88 (dd, J_1 = 19.6 Hz, J_2 = 4.7 Hz, 1H), 2.18 (m, 2H), 2.37 (s, 3H), 2.65 (m, 1H), 3.28 (m, 1H), 3.75 (s, 3H), 3.83 (m, 1H), 6.83 (m, 1H); ^{13}C NMR δ: 30.1 (CH_2), 31.6 (CH_2), 34.5 (CH_2), 36.8 (CH), 51.8 (NCH_3), 57.0 (OCH_3), 134.0 (C), 136.2 (CH), 166.7 (CO); MS (CI (NH_3)) m/z: 182 (100), 181 (15.6), 152 (15.3).

Synthesis of chiral amines

(*S*)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine **18***a*, which was the precursor to base **18**, was purchased from Aldrich and dried prior to use (CaH_2). Amines used for generating **21–24** were synthesized by methods reported in the literature (23). Amines that were the source of compounds **19** and **20** were synthesized by reductive amination (see below).

*(+)-(1S, 2S, 5S)-*N*-Phenyl-4,6,6-trimethylbicyclo[3.1.1]hept-3-enylamine (**19**a)*

Aniline (9.0 mmol; 0.83 g), and glacial acetic acid (15 mL) were placed under argon. (1*S*)-(−)-Verbenone (1.0 mmol; 0.154 mL) was then slowly added to this solution at room temperature and the reaction mixture was stirred for 4 h. Sodium borohydride (5.3 mmol; 200 mg) was then added in small portions and the turbid mixture was stirred at room temperature overnight under argon. Aqueous HCl solution (10%) was added to acidify the mixture, and acetic acid was then removed on a rotary evaporator. The residue was dissolved in chloroform (10 mL) and aqueous sodium carbonate solution (40%) was added until the mixture became basic. The mixture was then extracted with chloroform (4 × 20 mL). After washing with water, the combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed and the crude product was purified by chromatography (SiO_2, 4:1 *n*-hexane:ethyl acetate). Yield: 191 mg, $[\alpha]_D^{20}$ + 25.0 (*c* 0.0162 g/mL, $CHCl_3$); IR (KBr): 3429, 3049, 2922, 2867, 1600, 1502, 1428, 746, 691 cm^{-1}; ^{1}H NMR δ: 7.17 (td, J_1 = 7.4 Hz, J_2 = 1.0 Hz, 2H), 6.68 (t, J = 6.4 Hz, 1H), 6.60 (d, J = 7.7 Hz, 2H), 5.38 (br, 1H), 4.30 (br, 1H), 3.90 (br, 1H (NH)), 2.50 (m, 1H), 2.43 (m, 1H), 2.01 (t, J = 6.2 Hz, 1H), 1.74 (t, J = 1.8 Hz, 3H), 1.41 (d, J = 8.8 Hz, 1H), 1.32 (s, 3H), 1.07 (s, 3H); ^{13}C NMR δ: 147.8 (C), 147.5 (C), 130.1 (CH), 118.4 (CH), 117.5 (CH), 113.5 (CH), 56.5 (CH), 47.8 (CH), 45.2 (CH), 39.0 (CH_2), 35.0 (CH_2), 27.0 (CH_3), 23.0 (CH_3), 22.8 (CH_3); MS (CI (NH_3)) m/z: 229 (14.6), 228 (77.5), 227 (13.2), 135 (50.1), 94 (100.0). Anal. calcd. for $C_{16}H_{21}N$: C 84.53, H 9.31, N 6.16; found: C 84.40, H 9.02, N 6.15.

*(−)-(1R), 2R, 5S)-*N*-Phenyl-6,6-dimethylbicyclo[3.1.1]-heptanylamine (**20**a)*

Analogous procedure using (1*R*)-(+)-nopinone (1.0 mmol) and aniline yielded a yellowish oil, **20***a* (204 mg, 95%). After purification by flash chromatography, a colorless liquid was obtained (189 mg; 88%): bp 302°C; $[\alpha]_D^{20}$ −75.3 (*c* 0.1142 g/mL, $CHCl_3$); IR (KBr): 3421, 3050, 2911, 2867, 1601, 1502, 1465, 1315, 746, 691 cm^{-1}; ^{1}H NMR δ: 7.15 (t, J = 7.5 Hz, 2H), 6.65 (t, 7.3 Hz, 1H), 6.34 (d, J = 8.5 Hz, 2H), 3.94 (m, 1H), 3.81 (br, 1H (NH)), 2.28–2.48 (m, 2H), 2.19 (br, 1H), 1.98 (m, 2H), 1.88 (m, 1H), 1.61 (m, 1H), 1.21 (s, 3H), 1.12 (s, 3H), 1.03 (d, J = 10.0 Hz, 1H); ^{13}C NMR δ: 23.2 (CH_3), 24.7 (CH_2), 25.2 (CH_2), 27.8 (CH_3),

30.0 (C), 38.0 (CH_2), 41.1 (CH), 45.6 (CH), 54.9 (CH), 113.1 (CH), 116.9 (CH), 129.4 (CH), 147.6 (C); MS (CI (NH_3)) *m/z*: 217 (17.2), 216 (100); Anal. calcd. for $C_{15}H_{21}N$: C 83.67, H 9.83, N 6.50; found: C 83.77, H 9.71, N 6.47.

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