Enantioselective ring opening of tropinone. A new entry into tropane alkaloids

Marek Majewski, Ryszard Lazny, and Agnieszka Ulaczyk

Abstract: The lithium enolate of tropinone reacts with alkyl chloroformates to give 6-*N*-carboalkoxy-*N*-methyl-2-cycloheptenones (**4**). These compounds can be produced enantioselectively, in up to 95% ee, if chiral lithium amides (derived from optically pure amines **5**–**7**) are used for deprotonation of tropinone in the presence of additives. The effect of additives such as LiCl, LiBr, LiF, $LiClO_4$, $CeCl_3$, $ZnCl_2$, LiOH, TMEDA, HMPA, and DMPU on enantioselectivity of this deprotonation – ring opening sequence varies from slight to very large depending on the chiral amide – additive combination. Especially large increases in enantioselectivity are observed when the chiral, C2 symmetrical, lithium bis-α,α′-methylbenzylamide (Li-**5***a*) is used with one equivalent of LiCl. This reagent is best generated in situ from the corresponding amine hydrochloride and *n*-BuLi (2 equiv.). The ring-opening reaction combined with transposition of the carbonyl group (via Wharton reaction or allylic oxidation) provides a new method of stereoselective synthesis of tropane alkaloids having a protected hydroxyl at C-6 or C-7 (6β- and 7β-acetoxytropanes **14***a*, *b*) and physoperuvine (**19**).

Key words: enantioselective deprotonation, tropane alkaloids.

Résumé : L'énolate de lithium de la tropinone réagit avec les chloroformiates d'alkyles pour conduire à 6-*N*-carboalkoxy-*N*-méthylcyclopent-2-énones (**4**). Il est possible de produire ces composés avec une énantiosélectivité allant jusqu'à 95% ee si l'on utilise des amides de lithium chiraux (obtenus à partir des amines optiquement pures, **5**–**7**) pour effectuer la déprotonation de la tropinone, en présence d'additifs. L'effet de ces additifs, tels que LiCl, LiBr, LiF, $LiClO_4$, $CeCl_3$, $ZnCl_2$, LiOH, TMEDA, HMPA et DMPU, sur l'énantiosélectivité de cette séquence de déprotonation et d'ouverture de cycle peut être léger ou important suivant la nature de la combinaison de l'amide chiral et de l'additif. On observe des augmentations d'énantiosélectivité particulièrement importantes lorsqu'on utilise du bis-α,α′-méthylbenzylamide de lithium chiral, symétrique en C2 (Li-**5***a*), avec un équivalent de LiCl. Les meilleurs résultats sont obtenus en générant ce réactif in situ à partir du chlorhydrate de l'amine correspondant et du *n*-BuLi (2 équiv.). La réaction d'ouverture de cycle combinée avec la transposition du groupe carbonyle (via une réaction de Wharton ou une oxydation allylique) fournit une nouvelle méthode de synthèse stéréosélective des alcaloïdes du tropane comportant un groupe hydroxyle protégé en position C-6 ou C-7 (6β- ou 7β-acétoxytropanes, **14***a*, *b*) et de la physopéruvine (**19**).

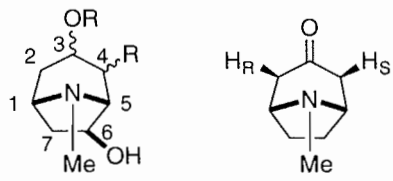
Mots clés : déprotonation énantiosélective, alcaloïdes du tropane.

[Traduit par la rédaction]

Introduction

Tropane alkaloids are a group of natural products isolated from plants (mainly of the *Solanaceae* family) and comprise over 200 compounds of which some 30% are chiral (1). This family of alkaloids includes some species famous (or infamous) for their biological activity, e.g., cocaine, atropine, scopolamine. Structurally, all tropane alkaloids contain the tropane (8-methyl-8-azabicyclo[3.2.1]octane) skeleton and a number of functional groups that, most often, are: a functionalized hydroxyl at C-3 (α or β), a side chain at C-2 or C-4 (α or β; the side chain is usually carbonyl based or is either an alkyl or a hydroxyalkyl group), and a β-hydroxyl at C-6 or C-7 (Fig. 1).

Fig. 1. Tropane alkaloids (**1**, generalized structure) and tropinone (**2**).



1 **2**

Tropinone (**2**) could be envisaged as a convenient starting material for synthesis of diverse tropane alkaloids provided that several stereoselectivity problems can be solved. A few years ago we began studying the enolate chemistry of tropinone with the aim of using this readily available symmetrical ketone as the starting material for synthesis of tropane alkaloids (2). During the early studies we established that tropinone lithium enolate (**3**), resulting from deprotonation of tropinone with LDA, undergoes a novel ring-opening reaction

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This paper is dedicated to Professor William A. Ayer on the occasion of his 65th birthday.

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Scheme 1.

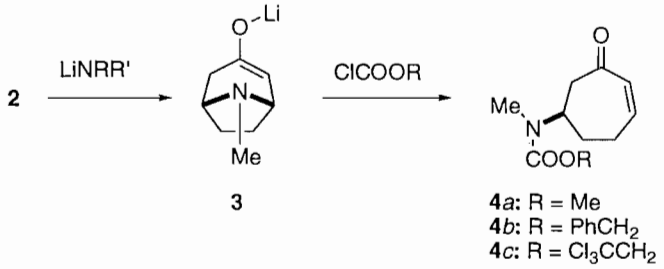
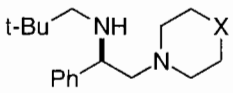


Fig. 2. Chiral amines used as precursors of the lithium amide bases.

5a: R'= Me; R"= Ph
5b: R'= R"= Me
5c: R'= R"= Ph
5d: R'=Me; R"= 1- naphtyl

6a: R = cyclohexyl
6b: R = 1-naphtyl



7a: X = CH_2
7b: X = NMe

upon treatment with a chloroformate (2*e*,*f*) to yield the substituted cycloheptenone **4** (Scheme 1). This compound can be produced enantioselectively when chiral lithium amides are used for deprotonation (3). Below, we describe the effects of additives on the enantioselectivity in this system and applications of the ring opening to the synthesis of physoperuvine and dihydroxytropanes.

Results and discussion

Our initial experiments with the deprotonation of tropinone using chiral lithium amides gave products in low enantioselectivity. We decided to evaluate several different bases and, since deprotonation reactions are often strongly affected by organic or inorganic additives (4) like lithium halides, amines (e.g., TMEDA), or by small amounts of polar cosolvents (e.g., HMPA, DMPU), we also used the chiral lithium amides in the presence of such additives.

Structures of chiral amines used as precursors for the chiral lithium amide bases in this study are shown in Fig. 2 and the experiments that involved deprotonation of **2** with these bases, followed by treatment of the resulting enolate with trichloroethyl chloroformate to give **4***c*, are summarized in Table 1. The dextrarotoatory isomer of **4***c* was the major product in all cases; the absolute stereochemistry of this isomer was established by correlation with anhydroecgonine (2*a*) and is as shown in Scheme 1. Most of the lithium amides tested gave low enantioselectivity in the absence of additives. The two exceptions were the lithiated bidentate amines **7***a*, *b* developed by Koga (5) that gave **4***c* in over 80% ee when the reaction was

Table 1. Formation of compound **4***c* (cf Scheme 1) using chiral lithium amides derived from chiral amines **5**, **6**, or **7**.

Entry	Lithium amide	Additive	ee[a] (%)	Yield[b] of **4***c* (%)
1	Li-**5***a*	—	44	80
2	Li-**5***a*	LiCl[c]	96	92
3	Li-**5***b*	—	29	80
4	Li-**5***c*	—	78	86
5	Li-**5***c*	LiCl[c]	87	65
6	Li-**5***d*	—	48	50
7	Li-**5***d*	LiCl[d]	88	89
8	Li-**6***a*	—	17	22
9	Li-**6***a*	LiCl[d]	72	60
10	Li-**6***b*	LiCl[d]	74	71
11	Li-**7***a*	—	83	82
12	Li-**7***a*	LiCl[c]	95	88
13	Li-**7***b*	—	87	80
14	Li-**7***b*	LiCl[c]	95	87

[a]The enantiomeric excess was determined by HPLC; cf. the experimental section.
[b]Yield of the purified compound **4***c* after column chromatography.
[c]One molar equivalent of LiCl with respect to **2** was used.
[d]Amine hydrochloride was used to generate the 1:1 Li-amide–LiCl complex.

run in THF (Table 1, entries 11 and 13). Addition of one equivalent of lithium chloride prior to enolization resulted in great enhancement of enantioselectivity when lithiated monodentate amines, and especially the C2 symmetrical amide Li-**a***a*, were used (Table 1, entries 1 and 2). Lithium chloride had a much smaller effect on the already efficient reactions involving the bidentate amides **7***a* and **7***b* (Table 1, entries 11 and 12, 13 and 14), but still caused the reaction selectivity, i.e., the k_{HS}/k_{HR} ratio, to increase by a factor of 2 (or greater).

Lithium amide derived from the C2 symmetrical amine **5***a* appeared to be the base of choice; the reagent used in the presence of LiCl was as efficient as Li-**7***a* or Li-**7***a*. The parent amines of the two latter compounds are much more difficult, and expensive, to make. We decided to investigate the effect of additives on the behavior of Li-**5***a* in greater detail: variable amounts of LiCl were tried as well as different lithium salts, salts of other metals, and also organic additives: TMEDA and cosolvents such as HMPA and DMPU. The results are summarized in Table 2.

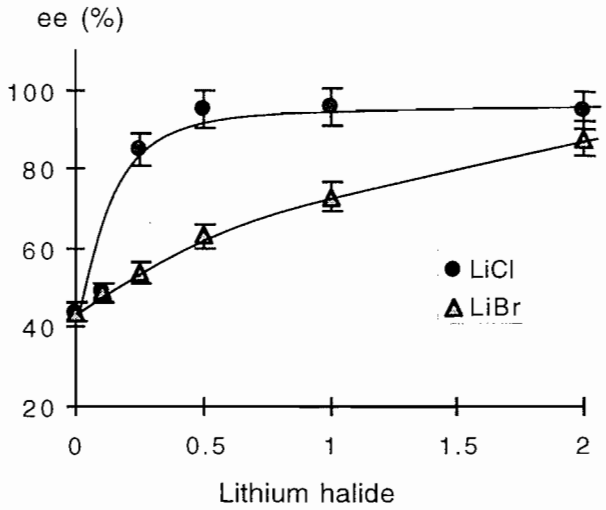
Addition of even small amounts of LiCl or LiBr resulted in an increase of enantioselectivity. The salt effects leveled off after one (LiCl) or two (LiBr) equivalents of the halide were added. The dependence of enantioselectivity on the number of equivalents of LiCl and LiBr is shown in Fig. 3. Lithium iodide, fluoride, or perchlorate had no effect on the selectivity of deprotonation. Cerium trichloride and zinc chloride showed salt effects similar to LiCl or LiBr but it should be noted that all our experiments with $ZnCl_2$ resulted in low yields. Organic additives, i.e., TMEDA, HMPA, and DMPU, had little effect. Interestingly, deliberate addition of water followed by the addition of the corresponding excess of BuLi (Table 2, entries 20 and 21; water and BuLi should translate into addition of 0.05 or 0.20 molar equivalent of LiOH, respectively) essen-

Table 2. The effect of additives on enantioselectivity of deprotonation of **2** with Li-**5***a*.

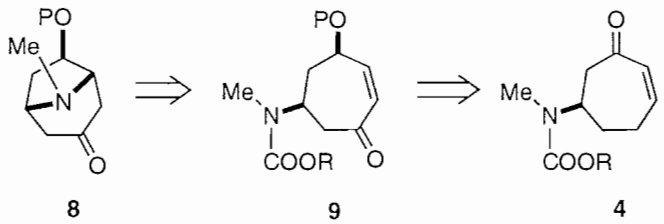
Entry	Additive (equiv.)	ee[a] (%)	Yield[b] of **4***c* (%)
1	—	44	80
2	LiCl (0.10)	49	84
3	LiCl (0.25)	85	92
4	LiCl (0.50)	95	90
5	LiCl (1.0)	96	92
6	LiCl (2.0)	95	94
7	LiBr (0.10)	49	78
8	LiBr (0.25)	54	82
9	LiBr (0.50)	63	88
10	LiBr (1.0)	73	93
11	LiBr (2.0)	88	85
12	LiF (1.0)	38	70
13	LiI (2.0)	41	78
14	$LiClO_4$ (1.0)	45	85
15	$CeCl_3$	80	70
16	$ZnCl_2$ (1.0)	87	40
17	TMEDA (1.0)	40	45
18	HMPA (1.0)	39	71
19	DMPU (1.0)	52	65
20	H_2O (0.05)[c]	24	48
21	H_2O (0.20)[c]	5	13

[a,b]See footnotes to Table 1.
[c]Excess BuLi (5% or 20%) was used in these experiments.

Fig. 3. Effect of LiCl and LiBr on enantioselectivity of formation of **4***c* (curves were fitted arbitrarily).



Scheme 2.



tially destroyed reaction selectivity and resulted in low yields. In all cases the yields were much lower than would be indicated by a simple assumption that a certain percentage of the base or the enolate was quenched. This underscores the need for thorough drying of the reagents and also the fact that it is not enough to titrate *n*-BuLi prior to use; if the reagent is contaminated with appreciable quantities of LiOH it will not work despite the reasonably high concentration of BuLi present. The great change in the reaction selectivity when a small amount of LiCl or LiBr was added precipitated the question of how halide-free was the commercial *n*-BuLi solution used in these experiments. This question was addressed by cyclic voltammetry: the amount of halide ions in a sample of *n*-BuLi hydrolyzed with MeOH was found to be smaller than 0.003 mole per mole of *n*-BuLi and thus could be assumed to have no effect on deprotonation.

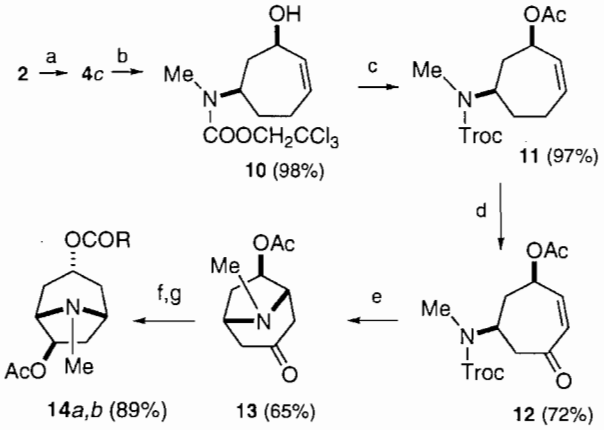
It appeared that some salts, and especially LiCl and LiBr, had a strong influence on enantioselectivity of deprotonation of tropinone with the amide Li-**5***a*. A similar (but shorter) study with the lithium amide Li-**7***a* revealed that addition of LiCl resulted in some increase in selectivity that was independent of the amount of LiCl in the 0.1–2.0 equivalent range (using 0.1 or 2.0 equiv. LiCl gave **4***c* in 94% ee in both cases); addition of HMPA had no effect (variable amounts of HMPA from 0.1 to 3.0 molar equivalents were tried) and addition of 0.20 molar equivalents of H_2O resulted in loss of selectivity and very low yields (6% ee and 8% yield of **4***c*).

It can be concluded that addition of one equivalent of LiCl greatly increases enantioselectivity of deprotonation of tropinone with some lithium amides. The amide Li-**5***a* used in the presence of one molar equivalent of LiCl is a very efficient reagent in this system. Lithium chloride can be easily generated in situ, and its is usually better to use the hydrochloride of the amine (e.g., **5***a*-HCl) with 2 molar equivalents of *n*-BuLi to obtain the required 1:1 amide–LiCl complex. In many cases the crystalline hydrochloride salts are easier to purify and to dry than the viscous liquid amines. The hydrochlorides are also much more stable than the parent amines (longer shelf life, especially in the presence of moisture, oxygen, and CO_2) and can be easily manipulated.

After elaborating the optimal conditions for the enantioselective ring-opening reaction the stage was set for applications of this method to synthesis of tropane alkaloids. A number of these natural products have a hydroxy group at C-6 (or C-7; alkaloid numbering) of the tropane skeleton (cf Scheme 1) and we thought that the ring opening could provide a good enantioselective entry into these systems. It should be noted that the amine **5***a* is available in both enantiomeric forms and thus the enantioselective ring-opening reaction, described above, provides a way to render either C-6 or C-7 allylic. However, we quickly found out that we were unable to either hydroxylate or brominate the γ position in the enone functional group of compound **4**, even after protecting the C=O groups as an acetal. In the end we developed a strategy for synthesis of 7β-acetoxy tropanes based on the 1,4-transposition of the carbonyl group in compound **4** (Scheme 2).

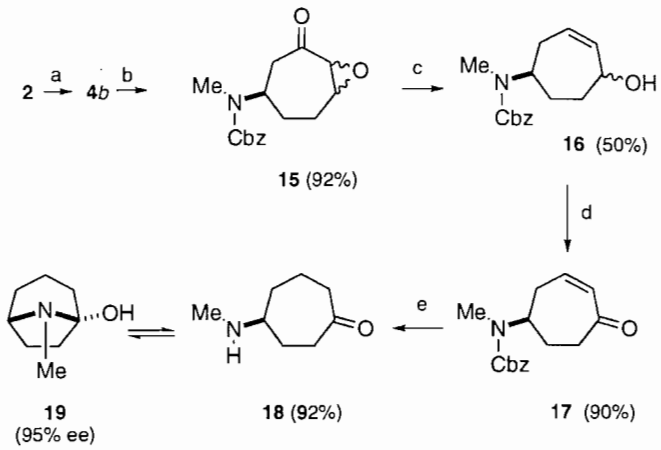
Enantioselective syntheses of two natural products, 7β-acetoxy-3α-tigloyloxytropane and 3α,7β-diacetoxytropane, are shown in Scheme 3. Reduction of the substituted cyclo-

Scheme 3.



a. (i) LiCl, **5***a*; (ii) ClCOOCHcCCl$_3$; b. NaBH$_4$, CeCl$_3$; c. Ac$_2$O, Et$_3$N, DMAP; d. (i) H$_2$SeO$_3$, (ii) PDC; e. Zn, EtOH; f. H2/PtO2; g. Ac$_2$O or Tg$_2$O

Scheme 4.



a. (i) LiCl, 5*a*; (ii) CbzCl; b. H$_2$O$_2$, KOH; c. NH$_2$NH$_2$; d. PDC; e. H$_2$/Pd

heptenone **4***c* proceeded selectively under conditions developed by Luche (6), i.e., with $CeCl_3$–$NaBH_4$. The allylic alcohol product **10** had to be protected before the oxidation was attempted. Several groups (e.g., 1-methoxy-1-methylethyl, TBDMS) were tried but failed to provide sufficient protection under typical allylic oxidation conditions (*t*-BuOOH–PDC, SeO_2). Finally the acetate **11**, which could lead directly to 7-acetoxy alkaloids, proved stable under these conditions. Another serious problem, however, was that none of the oxidants mentioned above was sufficiently effective. Best results were obtained with H_2SeO_3 in wet dioxane, but the reaction did not proceed beyond 15% conversion and produced a complex mixture of three oxidation products (two diasteroisomeric allylic alcohols and the enone **12**) and several unidentified byproducts. Increasing the reaction time, using an excess of the oxidant or adding the selenium reagent in small portions over a long time, did not improve the effectiveness of this process. However, after observing that substantial amounts of selenium were produced as a colloidal suspension, scavenging the selenium with Celite increased in the reaction yield significantly. To avoid dealing with the mixtures of allylic alcohols and the ketone **12** we decided on an oxidative work-up. Transformation of the acetate **11** to the enone **12** was finally accomplished in 72% yield by oxidation with H_2SeO_3–Celite followed by PDC (Scheme 3). Removal of the 2,2,2-trichloroethylcarbamate group from **12** with zinc in ethanol was followed by an immediate cyclization to give 7β-acetoxytropinone **13** in 95% ee. Scalemic **13** served as the key intermediate in the synthesis of two optically active tropane alkaloids: (+)-3α,7β-diacetoxytropane (**14***a*) and (−)-7β-acetoxy-3α-tigloyloxytropane (**14***b*). Stereoselective reduction of the carbonyl group in **13** was accomplished by hydrogenation over Adams' catalyst (Scheme 3).

A different transposition of the C=O group in **4** was used in the synthesis of physoperuvine **19** (Scheme 4). The cyclic hemiaminal functional group in this alkaloid can readily open (in fact physoperuvine exists in equilibrium with the ring-open form **18**) and, thus protected, 6-aminocycloheptenone **4** could be a precursor to **19** via a 1,3-transposition of the carbonyl group in the enone system. The Wharton reaction (7) provided a successful solution to this problem. Thus, after enantioselective deprotonation of tropinone with Li-**5***a*–LiCl (the lithium amide was generated in situ from the hydrochloride of **5***a*) and ring opening using benzyl chloroformate (CbzCl), the double bond in compound **4***b* was epoxidized using alkaline hydrogen peroxide. Although methanol is typically used as the solvent for epoxidation of enones, aqueous THF had to be used in this case to avoid the competing conjugate addition of methanol to **4***b*. The Wharton rearrangement was done by treatment of the mixture of two isomeric epoxides **15** with hydrazine and a catalytic amount of acetic acid. The rearranged allylic alcohol **16** was easily oxidized to the corresponding enone **17** using PDC. The ^{1}H NMR spectrum of this product is very similar to the spectrum of the enone **4***b*; however, a close examination of the spectra showed small differences in chemical shifts of the vinylic hydrogens, indicating that the two enones, **4***b* and **17**, are regioisomers. The transformation of this enone to physoperuvine (**19**) was precedented in the literature (8) but no experimental details were given. Hydrogenation of **17** provided the natural alkaloid, which exists predominantly in its hemiaminal form **19** (9).

Conclusions

Opening the five-membered ring of tropinone by deprotonation with a lithium amide base followed by treatment with a chloroformate was the source of protected 6-aminocycloheptenone **4**. The ketone can be produced enantioselectively by using chiral, nonracemic lithium amide bases for enantioselective deprotonation. The selectivity of this reaction depends on the structure of the base and on the reaction conditions (additives, cosolvents). The C2 symmetrical lithium amide Li-**a***a* generated in situ from the hydrochloride salt of the corresponding amine **5***a* and *n*-BuLi (2 equivalents) is the best reagent for this transformation. The ring-opening reaction was used for synthesis of physoperuvine **19** and two natural products from the 7β-acetoxytropane group (**14**).

Experimental part

All air-sensitive reactions were carried out under argon (10). Tetrahydrofuran was distilled under nitrogen from sodium and benzophenone. Diisopropylamine and other amines used as a

precursors for lithium amides were distilled from calcium hydride and stored over 4 Å molecular sieves. Chiral amines were prepared as described previously (11). Lithium chloride, bromide, and iodide were dried at 130–150°C under vacuum for 12 h and lithium perchlorate was dried (melted) at 200°C in an over for 12 h. The salts were then dissolved in THF and stored under argon. Butyllithium (*n*-BuLi solution in hexanes, Aldrich) was periodically titrated using 2,5-dimethoxybenzyl alcohol as the indicator. Tetramethylethylenediamine (TMEDA), hexamethylphosphoric triamide (HMPA), and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) were distilled from calcium hydride.

Flash column chromatography (FCC) (12) and dry-column flash chromatography (DFC) (13) were carried out using Merck silica gel 60 (230–400 mesh) and Sigma silica gel type H (10–40 μm), respectively, and thin-layer chromatography (TLC) was performed on precoated glass plates (Merck, silica gel 60, F254). The spots were detected using UV light (254 nm), the Dragendorff reagent (14), or with a developing solution of phosphomolybdic acid and ceric sulfate followed by charring on a hot plate.

Optical rotation was measured on a Perkin Elmer 241 polarimeter (1 dm cell); all concentrations are given in g/100 mL. Mass spectra are reported as *m/z* ratio (relative intensity); electron impact (EI) ionization was accomplished at 70 eV and chemical ionization (CI) at 50 eV. Infrared (IR) spectra were recorded on a Biorad FTS-40 Fourier Transform interferometer by a diffuse reflectance cell method; only diagnostic peaks are reported. Gas chromatography was performed using a Hewlett Packard 5890A instrument fitted with a methyl silicone gum column (HP-1, 5 m × 0.53 mm) unless otherwise stated.

Chromatographic analyses of enantiomeric purity of compound **4***c* were done on a chiralpack AD column. The solvent used was 15:1 hexane:isopropanol at 0.8 mL/min flow rate, and the sample concentration was 1 mg/mL. Statistically estimated error was ±1% ee. It should be noted, however, that differences between any two different experiments could be larger; the critical parameter for good reproducibility (and higher ee) seems to be slow rate of addition of the ketone to the lithium amide.

To obtain a high signal-to-noise ratio, ^{1}H NMR spectra for analysis of the ee were recorded on 20–25 mg samples in 0.4 mL $CDCl_3$ in the presence of 20 mg of *S*-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (*S*-(+)-TFAE). Statistically estimated error of the measurement was ±2% ee.

Generation of nonracemic tropinone lithium enolate using chiral amine hydrochloride

A solution of *n*-BuLi in hexanes (2.49 M, 7.12 mL, 17.7 mmol) was added to a suspension of (*S,S*)-(−)-*N,N*-bis(1-phenylethyl)amine hydrochloride (2.307 g, 8.80 mmol) in THF (80 mL) at 0°C and the mixture was stirred for 45 min. After cooling to −78°C for 20 min, tropinone (1.112 g, 8 mmol) in THF (8 mL) was added via a syringe pump (over 105 min) and the resulting solution was stirred for 120 min.

6-[*N*-(2,2,2-Trichloroethoxy)carbonyl-*N*-methyl]amino-2-cyclohepten-1-one (4*c*)

2,2,2-Trichloroethyl chloroformate (0.16 mL, 0.246 g, 1.16 mmol) was added to a solution of tropinone lithium enolate (1 mmol) at −78°C and the mixture was stirred for 30 min. After quenching with 40% K_2CO_3 (4 mL) and warming to room temperature (rt), the reaction mixture was extracted with ether (3 × 10 mL). The extracts were washed with 5% H_2SO_4 (to remove the chiral amine, 98% recovery) and brine, and were then dried ($MgSO_4$). The solvent was removed under vacuum to give the crude scalemic product, which was purified by crystallization from 5 mL of hexane (white solid, 0.289 g, 92%). The chiral amine was left in the mother liquor; mp (racemic): 59–61°C; mp (scalemic): 89–90°C; $[\alpha]_D^{26}$ +55.4 (*c* 1.05, MeOH), second crystallization +56.5 (*c* 1.04, MeOH); IR: 1713 (C=O), 1666 (C=O) cm^{-1}; ^{1}H NMR: 6.64 (ddd, *J* = 12 Hz, *J* = 6 Hz, *J* = 5 Hz, 1H), 6.05 (d, *J* = 12 Hz, 1H), 4.75 (s, 2H), 4.55 (br, 1H), 2.90 (s, 3H), 2.92–2.82 (m, 2H), 2.68–2.45 (m, 2H), 2.20–1.90 (m, 2H); ^{13}C NMR: 200.0, 154.0, 146.4, 132.4, 95.5, 75.0, 51.8, 47.9, 30.6, 29.3, 27.7 (some signals appeared as two peaks of unequal height due to amide isomerism); MS (EI): 315 (4), 313 (4), 124 (29), 108 (100), 109 (38), 82 (59), 81 (31), 80 (20). Anal. calcd. for $C_{11}H_{14}NO_3Cl_3$: C 41.99, H 4.48, N 4.45; found: C 42.-0, H 4.37, N 4.26.

(1*R*,6*R*)-6-[*N*-(2,2,2-Trichloroethoxy)carbonyl-*N*-methyl]amino-2-cyclohepten-1-ol (10)

A solution of $CeCl_3 \cdot 7H_2O$ (2.73 g, 7.32 mmol) in MeOH (15 mL) was added to an ice-cooled solution of the enone **4***c* (2.302 g, 7.33 mmol) in MeOH (25 mL). Solid $NaBH_4$ (0.280 g, 7.37 mmol) was added in small portions to the solution over 45 min. The reaction mixture was warmed up to rt (TLC showed absence of the starting material) and most of the solvent was removed under vacuum. The residue was treated with aqueous K_2CO_3 (2 g in 200 mL) and was extracted with CH_2Cl_2 (3 × 30 mL). The extracts were washed with water and brine, and were dried ($MgSO_4$). The solvent was removed under vacuum and the crude product (2.293 g, 99%) was used in the next step. An analytical sample was obtained by DFC (4:1 hexane–AcOEt). Properties: colorless oil, R_f = 0.56 (1:1 hexane–AcOEt); $[\alpha]_D^{26}$ +17.4 (*c* 1.32, MeOH); IR: 3453 (OH), 1711 (CO) cm^{-1}; ^{1}H NMR: 5.82–5.68 (m, 2H), 4.80–4.70 (m, 2H), 4.45–4.38 (m, 1H), 4.30–4.12 (m, 1H), 2.88 (s, 3H), 2.35–2.18 (m, 1H), 2.10–1.68 (m, 4H), 1.62–1.45 (m, 1H); ^{13}C NMR: 153/7, 138.6, 127.7, 95.4, 74.7, 68.1, 55.8, 40.5, 30.2, 28.4, 24.7; MS (EI): 300 (3), 397 (11), 234 (11), 232 (12), 149 (14), 110 (28), 92 (37), 84 (100). Anal. calcd.: C 41.72, H 5.09, N 4.42; found: C 41.97, H 5.13, N 4.31.

(1*R*,6*R*)-1-Acetoxy-6-[*N*-(2,2,2-trichloroethoxy)carbonyl-*N*-methyl]amino-2-cycloheptene (11)

A solution of the allylic alcohol **10** (2.200 g, 6.96 mmol) in CH_2Cl_2 (6 mL) and Et_3N (4 mL) containing DMAP (0.02 g) was cooled to 0°C. Acetic anhydride (1.0 mL, 10.6 mmol) was added and the reaction mixture was left at rt for 24 h. The reaction mixture was then shaken with aqueous K_2CO_3 (1.5 g in 20 mL) for 20 min, diluted with water (30 mL), and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with water (90 mL), dried ($MgSO_4$), and concentrated under vacuum. The residue was subjected to DFC (5–10% AcOEt–hexane), which gave the pure product as a colorless oil (2.410 g, 97%); R_f = 0.79 (1:1 hexane–AcOEt); $[\alpha]_D^{26}$ +16.7 (*c* 1.05, MeOH); IR: 1714, 1739 cm^{-1}; ^{1}H NMR: 5.88–5.25 (m, 1H), 5.65 (d, *J* = 12 Hz, 1H), 5.48–5.37 (m, 1H), 4.90–4.68 (m, 2H), 4.45–4.15 (m, 1H), 2.88 (s, 3H), 2.39–2.20 (m, 1H), 2.07

(s, 3H), 2.18–1.72 (m, 4H), 1.68–1.48 (m, 1H); ^{13}C NMR: 169.9, 153.8, 134.7, 129.4, 95.8, 75.0, 71.1, 56.2, 37.1, 30.5, 28.9, 24.9, 21.2; MS (EI): 359 (5), 357 (5), 324 (65), 322 (100), 318 (31), 317 (28), 316 (86), 315 (34), 314 (88). Anal. calcd.: C 43.53, H 5.06, N 3.90; found: C 43.56, H 5.13, N 3.92.

(4*R*,6*S*)-4-Acetoxy-6-[*N*-(2,2,2-trichloroethoxy)carbonyl-*N*-methyl]amino-2-cyclohepten-1-one (12)

A solution of H_2SeO_3 (0.942 g, 7.32 mmol) in wet dioxane (35 mL dioxane + 0.4 mL water) was added to a stirred mixture of allylic acetic **11** (2.399 g, 6.70 mmol), Celite (9 g), and dioxane (30 mL). The resulting mixture was refluxed with stirring for 18 h, diluted with EtOH (30 mL), and refluxed for a further 10 min. The black mixture was then filtered through Celite and the solvents were removed under vacuum. The residue was dissolved in 10% MeOH – CH_2Cl_2 and filtered through TLC-grade silica. Solvents were thoroughly removed from the filtrate and the residue was treated with CH_2Cl_2 (45 mL) and PDC (5.64 g, 15 mmol) for 12 h. The reaction mixture was then diluted with Et_2O (100 mL) and filtered through Celite/Florisil. The solvents were removed under vacuum and the residue was subjected to DFC (15–20% AcOEt – hexane), which provided the recovered starting material (0.963 g, 40%) and the product (1.086 g, 44%, 73% yield based on recovered starting material). Properties: colorless oil, R_f = 0.62 (1:1 hexane–AcOEt); $[\alpha]_D^{26}$ +22.5 (*c* 1.52, MeOH); IR: 1739, 1715, 1670 cm^{-1}; ^{1}H NMR: 6.48 (dd, *J* = 12.5 Hz *J* = 4 Hz, 1H), 6.03 (dd, *J* = 12 Hz, *J* = 4 Hz, 1H), 5.55 (br d, *J* = 12 Hz, 1H), 4.65 (s, 2H), 4.65–4.50 (m, 1H), 2.87 (s, 3H), 2.98–2.75 (m, 2H), 2.35–2.08 (m, 2H), 2.05 (s, 3H); ^{13}C NMR: 198.3, 169.5, 153.8, 144.9, 131.2, 95.3, 75.0, 69.2, 48.7, 47.5, 36.7, 29.6, 20.8; MS (CI-NH_3): 374 (10), 372 (10), 282 (34), 280 (54), 279 (30), 198 (44), 140 (100), 107 (50), 61)50). Anal. calcd.: C 41.90, H 4.38, N 3.76; found: C 41.77, H 4.28, N 3.63.

(−)-7β-Acetoxytropinone (13) (ref. 15)

A mixture of the enone **12** (1.030 g, 2.77 mmol) and zinc powder (3.9 g) in 95% EtOH (60 mL) was refluxed for 2 h (TLC showed the absence of the starting material). Most of the solvent was removed under vacuum and the residue was treated with 25% aqueous NH_3 (2 mL), CH_2Cl_2 (80 mL), Celite, and $MgSO_4$. The resulting suspension was filtered, the solvent was evaporated under vacuum, and the residue was subjected to DFC (2% MeOH – CH_2Cl_2). A yellowish oil was obtained (0.382 g, 70%). Kugelrohr distillation (at 120°C/0.5 Torr (lit. (16) bp 110°C/0.03 Torr); 1 Torr = 133.3 Pa) gave the pure product (0.354 g, 65%); R_f = 0.35 (3% MeOH in CH_2Cl_2), R_f = 0.60 (10% MeOH in CH_2Cl_2); $[\alpha]_D^{26}$ −20.2 (*c* 1.10, MeOH), 95% ee *S*-(+)-TFAE; IR: 1713, 1732 cm^{-1}; ^{1}H NMR: 4.88 (dd, *J* = 4, 6.5 Hz, 1H), 3.60 (br s, 1H), 3.46 (br d, 1H), 2.70 (d, *J* = 5 Hz, 1H), 2.64 (d, *J* = 5 Hz, 1H), 2.60 (s, 3H), 2.30 (d, *J* = 16.5 Hz, 1H), 2.18–2.08 (m, 3H), 2.01 (s, 3H); ^{13}C NMR: 206.9, 170.3, 77.6, 65.6, 59.3, 44.2, 42.0, 37.3, 35.8, 20.8.

(+)-7β-Acetoxy-3α-hydroxytropane (13*a*) (ref. 15)

A solution of the ketone **14** (0.298 g, 1.51 mmol) in 95% EtOH (18 mL) with PtO_2 (0.03 g) was hydrogenated in a Paar apparatus at 50 psi (1 psi = 6.9 kPa) and at rt for 12 h. The mixture was filtered through Celite and the solvent was removed under vacuum. A yellowish oil was obtained (0.290 g, 97%). An analytical sample was purified through DFC; R_f = 0.13 (10% MeOH in CH_2Cl_2); $[\alpha]_D^{26}$ +21.3 (*c* 1.05, MeOH); IR: 3162, 1733 cm^{-1}; ^{1}H NMR: 5.63 (dd, *J* = 3, 7.5 Hz, 1H), 4.09 (t, *J* = 5 Hz, 1H), 3.39–3.30 (m, 1H), 3.18 (br s, 1H), 2.90 (br, 1H), 2.74 (dd, *J* = 7.5, *J* = 14 Hz, 1H), 2.53 (s, 3H), 2.26–2.03 (m, 3H), 2.06 (s, 3H), 1.79 (d, *J* = 15 Hz, 1H), 1.58 (d, *J* = 15 Hz, 1H); ^{13}C NMR: 171.0, 79.3, 65.4, 63.5, 59.3, 38.3, 36.0, 35.0, 34.1, 21.2.

(+)-3α,7β-Diacetoxytropane (14*a*) (refs. 16, 17)

A solution of the alcohol **13*a*** (0.127 g, 0.638 mmol) in CH_2Cl_2 (0.5 mL) and Et_3N (0.5 mL) containing DMAP (0.005 g) was treated with Ac_2O (0.097 g, 0.95 mmol) and the reaction mixture was left at rt for 24 h. The reaction mixture was then shaken with aqueous K_2CO_3 for 10 min, diluted with water (10 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The extracts were dried ($MgSO_4$) and evaporated under vacuum. The residue was subjected to DFC (3–6% MeOH – CH_2Cl_2), which gave the pure product as a colorless oil (0.143 g, 93%); R_f = 0.42 (10% MeOH – CH_2Cl_2); $[\alpha]_D^{26}$ +15.5 (*c* 1.04 EtOH) (lit. (16) $[\alpha]_D^{26}$ (enantiomer) −16.6; 96% optical purity); IR: 1734 cm^{-1}; ^{1}H NMR: 5.45 (dd, *J* = 3, 7.5 Hz, 1H), 5.04 (t, *J* = 5 Hz, 1H), 3.43–3.34 (m, 1H), 3.22 (s br, 1H), 2.57 (dd, *J* = 7.5, 14 Hz, 1H), 2.55 (s, 3H), 2.32–2.05 (m, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 1.83 (d, *J* = 15.5 Hz, 1H), 1.61 (d, *J* = 15.5 Hz, 1H); ^{13}C NMR: 170.4, 169.5, 78.5, 66.4, 64.6, 58.7, 38.0, 35.7, 32.2, 30.6, 21.0, 20.8.

(−)-7β-Acetoxy-3α-tigloyloxytropane (14*b*) (refs. 18, 19)

The alcohol **13*a*** (0.100 g, 0.502 mmol) was dissolved in dry pyridine (1.2 mL) and dry benzene (0.6 mL), and treated with DMAP (0.026 g) and tigloic anhydride (Tg_2O; 0.2 g, 1.1 mmol) for 3.5 days. The mixture was then diluted with $CHCl_3$ shaken with aqueous K_2CO_3 solution, and extracted with $CHCl_3$ (3 × 20 mL). The extracts were washed with water, dried ($MgSO_4$), and the solvent was removed under vacuum. The residue was subjected to DFC (1% MeOH – CH_2Cl_2 eluted unreacted anhydride, 3% eluted with product), which gave the pure product as a colorless oil (0.130 g, 92%); R_f = 0.47 (10% MeOH – CH_2Cl_2); $[\alpha]_D^{25}$ −14.6 (*c* 2.03, EtOH) (lit. (18) $[\alpha]^{20}$D −11.5 (*c* 12.4, EtOH); −9.0 (*c* 1.55, $CHCl_3$) (lit. (19) $[\alpha]_D^{19}$ −13 ($CHCl_3$); IR: 1734, 1707, 1650 cm^{-1}; ^{1}H NMR: 6.91 (tt, *J* = 1, 7 Hz, 1H), 5.50 (dd, *J* = 3, 7.5 Hz, 1H), 5.23 (t, *J* = 5 Hz, 1H), 3.45–3.36 (m, 1H), 3.26 (s br, 1H), 2.63 (dd, *J* = 14, *J* = 7.5 Hz, 1H), 2.57 (s, 3H), 2.36–2.22 (m, 2H), 2.20–2.10 (m, 1H), 2.08 (s, 3H), 1.89 (s, 3H), 1.84 (dd, *J* = 7 Hz, *J* = 1 Hz, 3H), 1.65 (br d, *J* = 15 Hz, 1H); ^{13}C NMR: 170.4, 166.5, 137.2, 128.3, 78.5, 66.2, 64.5, 58.8, 38.1, 36.1, 32.4, 30.9, 20.8, 14.1, 11.6.

5-(*N*-Benzyloxycarbonyl-*N*-methyl)amino-2-cyclohepten-1-one (4*b*)

Benzyl chloroformate (0.17 mL, 0.204 g, 1.20 mmol) was added to a solution of tropinone lithium enolate (1 mmol) at −78°C and the mixture was stirred for 30 min. After quenching with 40% K_2CO_3 (4 mL) and warming to rt, the reaction mixture was extracted with ether (3 × 10 mL). The extracts were washed with 5% H_2SO_4 (to remove the chiral amine, 98% recovery) and brine, and were dried ($MgSO_4$). The solvent was removed under vacuum to give the crude product, which was subjected to chromatographic purification by DFC

(5–50% hexane – AcOEt, R_f = 0.43 in 1:1 hexane–AcOEt). The product was obtained as a colorless oil (0.232 g, 85%); $[\alpha]_D^{24}$ +70.0 (*c* 1.04, MeOH); IR: 1697, 1666 cm^{-1}; ^1H NMR: 7.35–7.20 (m, 5H), 6.64 (ddd, *J* = 12 Hz, *J* = 6 Hz, *J* = 5 Hz, 1H), 6.05 (d, *J* = 12 Hz, 1H), 5.13 (s, 2H), 4.50 (br, 1H), 2.90–2.80 (m, 2H), 2.85 (s, 3H), 2.65–2.40 (m, 2H), 2.12–1.88 (m, 2H); ^{13}C NMR: 200.2, 155.5, 146.2, 136.5, 132.3, 128.3, 127.8, 127.6, 67.0, 51.2, 48.0, 30.8, 29.2, 27.6; MS (EI): 273 (1), 167 (11), 138 (23), 110 (20), 107 (11), 92 (21), 91 (100), 65 (17). Anal. calcd. for $C_{16}H_{19}NO_3$: C 70.31, H 7.01, N 5.12; found: C 70.16, H 7.83, N 5.07.

(−)-6-(*N*-Benzoyloxycarbonyl-*N*-methyl)amino-2,3-epoxycycloheptan-1-one (15)

Compound **4***b* (1.215 g, 4.45 mmol) was dissolved in a mixture of THF (20 mL) and water (5 mL), and the solution was cooled to ca. −10°C (ice–acetone bath). A hydrogen peroxide solution (30%, 3 mL, 26 mmol), followed by a solution of KOH (0.05 g, 0.9 mmol) in water (2 mL), was added to the stirred mixture. After min the reaction mixture was warmed to rt and was further stirred for 15 min. TLC showed absence of the starting material. The reaction mixture was diluted with water (80 mL) and was extracted with $CHCl_3$ (4 × 40 mL). The extracts were dried ($MgSO_4$), the solvent removed under vacuum, and the residue was subjected to DFC. a mixture of two isomeric epoxides (3:1) was obtained (1.20 g, 93%) as a colorless oil (major isomer R_f = 0.53, minor isomer R_f = 0.44 in 1:1 hexane–AcOEt); $[\alpha]_D^{24}$ −48 (*c* 1.1, MeOH), major isomer; IR: 1703 cm^{-1}; ^1H NMR: 7.43–7.30 (m, 5H), 5.16 (s, 2H), 4.05–3.75 (m, br, 1H), 3.46–3.42 (m, 2H), 3.20 (t, *J* = 12 Hz, 1H), 2.85 (s, 3H), 2.44–2.40 (m, 1H), 2.34 (d, *J* = 10 Hz, 1H), 2.28–2.22 (m, 1H), 2.10–1.90 (m, 1H), 1.70–1.60 (m, 1H); ^{13}C NMR: 206.7, 155.0, 136.2, 128.0, 127.6, 127.4, 66.8, 58.8, 55.3, 51.8, 44.2, 28.0, 27.0, 24.3; MS (EI): 289 (4), 146 (30), 111 (9), 92 (100), 83 (12), 65 (11), 57 (11), 55 (7); HRMS: 289.132 (M^+); calcd. for $C_{16}H_{19}NO_4$: 289.131.

(−)-5-(*N*-Benzyloxycarbonyl-*N*-methyl)amino-2-cyclohepten-1-ol (16)

The epoxide **15** (1.00 g, 3.46 mmol) was dissolved in dry MeOH and a solution of hydrazine (0.34 g, 19.6 mmol in 5 mL of MeOH dried with 3Å molecular sieves) was added at rt with stirring. After addition of glacial AcOH (2 drops), stirring was continued for another 2 h (N_2 evolved and the reaction mixture warmed up slightly). The resulting solution was then diluted with $CHCl_3$ (25 mL) and was washed with 5% H_2SO_4. The acid washings were extracted with $CHCl_3$ (3 × 20 mL). The combined extracts were dried ($MgSO_4$), filtered through a small pad of TLC-grade silica, and the solvent was removed under vacuum. The resulting residue was subjected to DFC (35–50% AcOEt in hexane). A mixture of two isomers was obtained (0.476 g, 50%). Major isomer R_f = 0.32, minor isomer R_f = 0.27 (1:1 hexane–AcOEt); $[\alpha]_D^{24}$ −66 (*c* 1.1, MeOH), major isomer; IR: 3415, 1695, 1677 cm^{-1}; ^1H NMR: 7.40–7.25 (m, 5H), 5.85–5.10 (m, 2H), 5.13 (s, 2H), 4.50–4.10 (m, 1H), 2.80 (s, 3H), 2.52–2.45 (m, 2H), 2.35 (d, *J* = 10 Hz, 1H), 2.20–2.08 (m, 1H), 2.07–1.70 (m, 4H); ^{13}C NMR: 155.7, 135.0, 128.3, 127.8, 127.7, 127.6, 124.9, 71.5, 68.5, 66.9, 54.2, 53.7, 35.4, 32.3; MS ($CI0NH_3$): 276 (20), 274 (11), 259 (18), 258 (100), 168 (17), 166 (27), 108 (28), 91 (65); HRMS: 275.152 (M^+); calcd. for $C_{16}H_{21}NO_3$: 275.152.

(5*R*)-5-(*N*-Benzyloxycarbonyl-*N*-methyl)amino-2-cyclohepten-1-one (17) (ref. 8)

A solution of the alcohol **16** (0.448 g, 1.63 mmol) in CH_2Cl_2 (25 mL) was treated with PDC (0.94 g, 2.50 mmol) for 12 h at rt. The reaction mixture was diluted with Et_2O (75 mL) and filtered through a pad of Celite and TLC-grade silica (washed with 1:1 hexane–AcOEt). After removing the solvents the crude product was obtained as a colorless oil (0.400 g, 90%); R_f = 0.35 (1:1 hexane–AcOEt); $[\alpha]_D^{25}$ +93 (*c* 1.0, MeOH); IR: 1693, 1679 cm^{-1}; ^1H NMR: 7.42–7.25 (m, 5H), 6.57 (ddd, *J* = 12 Hz, *J* = 6.5 Hz, *J* = 5 Hz, 1H), 6.07 (d, *J* = 12 Hz, 1H), 5.13 (s, 2H), 4.50 (br, 1H), 2.89 (s, 3H), 2.80–2.53 (m, 4H), 2.09–1.85 (m, 2H); ^{13}C NMR: 201.7, 155.1, 142.2, 136.2, 132.1, 128.0, 127.5, 127.3, 66.6, 54.2, 39.8, 33.3, 29.0, 25.0.

(+)-Physoperuvine (19) (refs. 4*c*, 4*d*, 20)

A solution of the enone **17** (0.340 g, 1.24 mmol) in MeOH (12 mL) was hydrogenated in the presence of 30% Pd/C (0.026 g) over 2 h at 30 psi in a Paar apparatus. The mixture was filtered through Celite and the solvent was removed under vacuum to provide an off-white solid (0.163 g, 92%). Analytically pure material was obtained through Kugelrohr sublimation (at 100–120°C/0.5 Torr). Properties: white solid, R_f = 0.66 (5:4:1 $CHCl_3$–MeOH – 25% aqueous NH_3); mp (racemic) 72–73°C (acetone) (lit. (21) mp 75°C); $[\alpha]_D^{25}$ +17.9 (*c* 1.30, H_2O), 95% ee with (*S*)-(+)-TFAE (lit. (21) $[\alpha]_D$ +1.2 (*c* 1.3, H_2O); mp (opt. active) 48–50°C (sublimed) (lit. (20) mp 47°48°C); IR: 3099 (OH) cm^{-1}; ^1H NMR: 3.13 (br s, 1H), 2.38 (s, 3H), 2.15–1.87 (m, 4H), 1.82–1.52 (m, 5H), 1.34–1.20 (m, 1H).

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References

1. (*a*) Recent review: M. Lounasmaa and T. Tamminen. The alkaloids **44**, 1 (1993); Physoperuvine: (*b*) A.T. McPhail and A.R. Pinder. Tetrahedron, **40**, 1661 (1984); (*c*) A.R. Pinder. J. Org. Chem. **47**, 3607 (1982); (*d*) M. Sahai and A.B. Ray. J. Org. Chem. **45**, 3265 (1980).
2. (*a*) M. Majewski and R. Lazny. J. Org. Chem. **60**, 5825 (1995); (*b*) Synlett, 785 (1996); (*c*) Tetrahedron Lett. **35**, 3653 (1994); (*d*) M. Majewski and G.-Z. Zheng. Can. J. Chem. **70**, 2618 (1992); (*e*). Synlett, 173 (1991); (*f*) This reaction had also been independently reported in a lecture: N.S. Simpkins. Chem. Soc. Rev. **19**, 335 (1990).
3. Enantioselective deprotonation was reviewed: (*a*) P.J. Cox and N.S. Simpkins. Tetrahedron: Asymmetry, **2**, 1 (1991); (*b*) M. Majewski. *In* Advances in carbanion synthesis. Vol. 3. *Edited by* V. Snieckus. JAI Press, Greenwich, Connt. In press.
4. (*a*) E. Juaristi, A.K. Beck, J. Hansen, T. Matt, T. Mukhopadhyay, M. Simson, and D. Seebach. Synthesis, 1271 (1993); (*b*) P.L. Hall, J.H. Gilchrist, and D.B. Collum. J. Am. Chem. Soc. **113**, 9571 (1991); (*c*) A. Loupy and B. Tchoubar. Salt effects in organic and organometallic chemistry. VCH, New York. 1991; (*d*) D. Seebach. Angew. Chem. Int. Ed. Engl. **27**, 1624 (1988), (*e*) D. Seebach, A.K. Beck, and A. Studer. *In* Modern synthetic methods. Vol. 7. *Edited by* B. Ernst and C.

Leumann. VCH, Weinheim. 1995; (*f*) P. Coggins, S. Gaur, and N.S. Simpkins. Tetrahedron Lett. **36**, 1545 (1995); (*g*) M. Majewski, R. Lazny, and P. Nowak. Tetrahedron Lett. **36**, 5465 (1995); (*h*) M. Toriyama, K. Sugasawa, M. Shindo, N. Tokutake, and K. Koga. Tetrahedron Lett. **38**, 567 (1997).
5. K. Koga. Pure Appl. Chem. **66**, 1487 (1994).
6. J.-L. Luche. J. Am. Chem. Soc. **100**, 2226 (1978).
7. P.S. Wharton and D.H. Bohlen. J. Org. Chem. **26**, 3615 (1961).
8. F.-D. Boyer, P.-H. Ducrot, V. Henryon, and J.-Y. Lallemand. Synlett, 357 (1992).
9. A.B. Ray, Y. Oshima, H. Hikino, and C. Kabuto. Heterocycles, **19**, 1233 (1982).
10. J. Leonard, B. Lygo, and G. Procter. Advanced practical organic chemistry. Chapman & Hall, New York. 1995.
11. (*a*) R. Shirai, K. Aoki, D. Sato, H.-D. Kim, M. Murakata, T. Yasukata, and K. Koga. Chem. Pharm. Bull. **42**, 690 (1994); (*b*) C.G. Overberger, N.P. Marullo, and R.G. Hiskey. J. Am. Chem. Soc. **83**, 1374 (1961); (*c*) H.M.R. Hoffmann, K. Haase, Z.M. Ismail, S. Preftitsi, and A. Weber. Chem. Ber. **115**, 3880 (1982); (*d*) J.F. Normant and C. Piechucki. Bull. Soc. Chim. Fr. **6**, 2402 (1972).
12. W.C. Still, M. Khan, and A. Mitra. J. Org. Chem. **43**, 2923 (1978).
13. L.M. Harwood. Aldrichimica Acta, **18**, 25 (1985).
14. G. Zweig and J. Sherma. Handbook of chromatography. Vol. 2. CRC Press, Boca Raton, Fla. 1972.
15. Y.Y. Lin and J.B. Jones. J. Org. Chem. **38**, 3575 (1973).
16. G. Fodor and F. Soti. Tetrahedron Lett. 1917 (1964).
17. A.J. Parr, J. Payne, J. Eagles, B.T. Chapman, R.J. Robins, and M. Rhodes. Phytochemistry, **29**, 2545 (1990).
18. W.C. Evans and A. Major. J. Chem. Soc. (C), 1621 (1966).
19. I.R.C. Bick, J.W. Gillard, H.-M. Leow, and N.W. Preston. Aust. J. Chem. **32**, 2071 (1979).
20. A.T. McPhail and A.R. Pinder. Tetrahedron, **40**, 1661 (1984).