DOI: 10.1002/ejoc.201101333

A Route to "all-*cis*" 2-Methyl-6-Substituted Piperidin-3-ol Alkaloids from *syn*-(2*R*,1′*S*)-2-(1-Dibenzylaminomethyl)epoxide: Rapid Total Synthesis of (+)-Deoxocassine

Pierre-Yves Géant,[a] Jean Martínez,[a] and Xavier J. Salom-Roig*[a]

Keywords: Alkaloids / Epoxides / Hydrazones / Amination / Total synthesis

A general strategy leading to the synthesis of two *cis*-2-methyl-6-substituted piperidin-3-ols is described. *syn*-(2*R*,1′*S*)-2-(1-Dibenzylaminomethyl) epoxide (**13**) was used as common building block. The key step involved oxirane ring opening of **13** by the nucleophilic lithium aza-enolate of hydrazones **12a** and **12b**. Subsequent hydrazone hydrolysis and intramolecular reductive amination afforded the alkaloid (+)-deoxocassine and a new C-6 ethyl analogue of this substance in good yields.

Introduction

cis-2-Methyl-6-substituted piperidin-3-ol alkaloids have been isolated from leaves and twigs of the plant genera *Cassia* and *Prosopis*.[1] Most of them have an "all-*cis*" relative configuration as a stereochemical feature. Structural diversity is due to a long side chain at C-6. Typical representatives of this class of compound include (+)-deoxocassine (**1**), (+)-cassine (**2**), (+)-prosafrinine (**3**), (+)-spectaline (**4**), (+)-spicigerine (**7**) azimine (**8**), and carpaine (**9**, Figure 1).[2] The last two compounds are symmetrical macrocyclic dilactones, which can be hydrolyzed to (+)-azimic acid (**5**) and (+)-carpamic acid (**6**).[3] Besides their interesting structural features, these compounds display a wide range of biological activities due to their ability to mimic carbohydrates in a variety of enzymatic processes.[4] In light of this, considerable effort has been invested into the development of syntheses of "all-*cis*" 2-methyl-6-substituted piperidin-3-ols. Although several syntheses based on a chiral pool approach[5] or the use of asymmetric synthesis[6] have been reported, they often do not allow for adequate diversity and substitution. The importance of this 2,3,6-trisubstituted piperidine scaffold makes short, efficient, and versatile access to C-6 analogues of "all-*cis*" 2-methyl-6-substituted piperidin-3-ols still attractive.

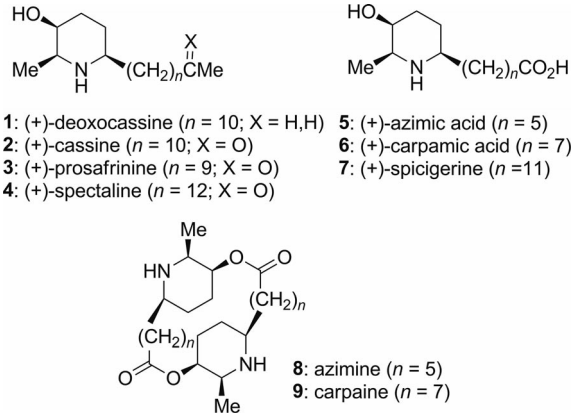


Figure 1. Structures of naturally occurring *cis*-2-methyl-6-substituted piperidin-3-ol alkaloids.

Herein, we describe a concise asymmetric general route to "all-*cis*" 2-methyl-6-substituted piperidin-3-ol alkaloids from *syn*-(2*R*,1′*S*)-2-(1-dibenzylaminomethyl) epoxide (**13**) as a common key building block.[7] This approach should be adaptable to the production of other structurally related alkaloids such as **2**–**7**. To demonstrate the synthetic interest of this methodology, we have realized the total synthesis of (+)-deoxocassine (**1**) and its C-6 ethyl-substituted analogue **10**.

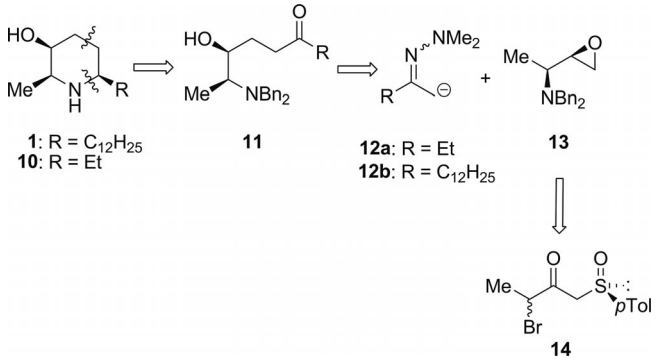
Results and Discussion

As depicted in Scheme 1, retrosynthetic analysis led us to dibenzylamino ketone **11**, which after debenzylation and concomitant intramolecular reductive amination, should lead to target piperidines **1** and **10**. In the key step of the synthesis, dibenzylamino ketone **11** was planned to be prepared in a one-pot procedure by ring opening of epoxide **13**, obtained from α-bromo-α′-(*R*)-sulfinylketone **14**, with the lithiated anion of hydrazones **12a** and **12b** and subsequent hydrazone hydrolysis.

[a] Institut de Biomolécules Max Mousseron (IBMM), UMR 5247,
Université de Montpellier I et II, CNRS,
Place Eugène Bataillon, 34095 Montpellier, France
Fax: +33-4-67144866
E-mail: salom-roig@univ-montp2.fr

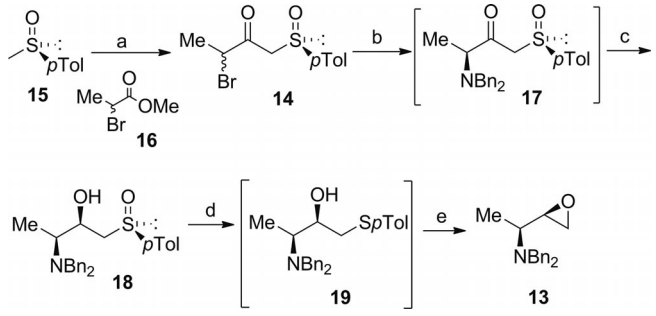
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201101333.

WILEY ONLINE LIBRARY © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



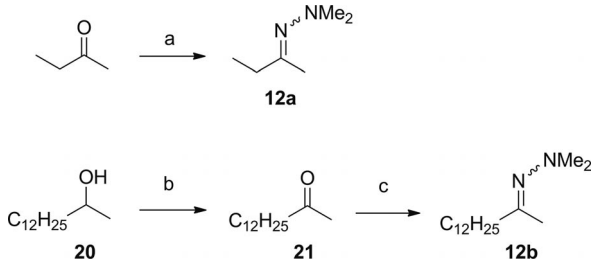
Scheme 1. Retrosynthetic pathway to piperidine derivatives **1** and **10**.

The synthesis of epoxide **13** was performed according to the path shown in Scheme 2 by using the methodology reported in an earlier study.[8] To the lithiated anion of (+)-(*R*)-methyl *p*-tolyl sulfoxide (**15**), obtained by using LDA as base at –78 °C, was added (±)-methyl 2-bromopropionate (**16**), which produced an epimeric mixture of α-bromo-α′-(*R*)-sulfinylketone **14** in 95% yield. The latter furnished ketone **17** through a combined in situ substitution–epimerization process, a so-called dynamic kinetic resolution. To reduce stereoselectively the carbonyl group, the resulting crude residue of derivative **17** was treated successively with ZnI_2, which chelated between the carbonyl group and the basic oxygen of the sulfoxide group, and then with DIBAL at –78 °C. Desired *syn*-amino alcohol **18** was obtained in two steps in 94% yield in multigram amounts and with excellent stereoselectivity (>95:5).[9] Thereafter, compound **18** was heated at reflux in $CHCl_3$ in the presence of an excess amount of *tert*-butyl bromide to afford the corresponding sulfide **19**.[10] The crude reaction mixture was then treated with Meerwein's salt (Me_3OBF_4), and the resulting sulfonium salt was treated with K_2CO_3 to afford, after purification by column chromatography on silica gel, key intermediate **13** in 78% yield along with methyl *p*-tolyl sulfide.[11]



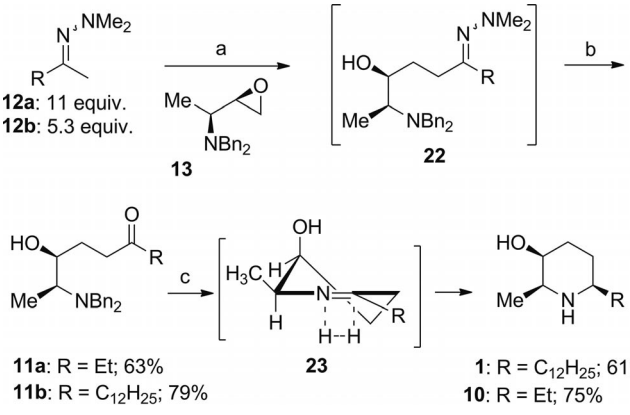
Scheme 2. Synthesis of compound **13**. Reagents and conditions: (a) LDA, THF, –78 °C, then **16**, 95%; (b) Bn_2NH, THF, r.t.; (c) ZnI_2, r.t., 30 min, then DIBAL-H, THF, –78 °C, 94% (two steps); (d) *t*BuBr, $CHCl_3$, reflux; (e) Me_3OBF_4, CH_2Cl_2, r.t., 5 h, then K_2CO_3, 78% (two steps).

With the necessary key building block in hand, we focused on the synthesis of the piperidine ring by coupling hydrazones **12a** and **12b** with oxirane **13**. The wide applicability of *N*,*N*-dimethylhydrazones in synthesis has been a subject of major importance in organic chemistry,[12] in particular in C–C bond formation. *N*,*N*-Dialkylhydrazones offer many advantages such as high nucleophilicity of their metalated species (particularly organolithium derivatives), regioselectivity, and controlled α-monoalkylation. Aza-enolates, usually formed by deprotonation with LDA, can react with quite a number of electrophiles. In particular, oxiranes have rarely been employed.[13] In this context, initial attention focused upon the preparation of the required dimethylhydrazones. 2-Butanone (Scheme 3) was then converted into its dimethylhydrazone **12a** in 82% yield by reaction with dimethyl hydrazine in refluxing CH_2Cl_2. Analogue **12b** was obtained by a two-step sequence starting from commercially available alcohol **20**. This derivative was oxidized by using PCC to the corresponding ketone **21** in 95% yield. Dimethylhydrazone **12b** was obtained in quantitative yield by using a procedure similar to that used for **12a**.



Scheme 3. Synthesis of *N*,*N*-dimethylhydrazones **12a** and **12b**. Reagents and conditions: (a) NH_2NMe_2, CH_2Cl_2, reflux, 82%; (b) PCC, CH_2Cl_2, 95%; (c) NH_2NMe_2, CH_2Cl_2, reflux, 100%.

Oxirane ring opening of **13** was achieved by addition to the aza-enolate of dimethylhydrazones **12a** or **12b** at room temperature (Scheme 4). A large excess of aza-enolate (11 equiv. for **12a** and 5.3 equiv. for **12b**), generated from the corresponding hydrazones and butyllithium at 0 °C, was required to reach a complete opening of oxirane **13**. The use of an excess amount of anhydrous LiCl as additive, according to a known literature procedure for enolate oxirane ring opening,[13d,14] did not improve the results. Exposure of the mixture of crude hydrazone **22** and the excess



Scheme 4. Synthesis of "all-*cis*" piperidine derivatives **1** and **10**. Reagents and conditions: (a) BuLi, THF, 0 °C to r.t. then **13**; (b) SiO_2, THF/H_2O; (c) H_2 (balloon), $Pd(OH)_2$/C, EtOH.

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

amount of hydrazones **12a** or **12b** to SiO_2, in a 1:1 mixture of water/THF, provided desired ketones **11a** and **11b** in 63 and 79% yield, respectively, in a one-pot procedure, after purification by column chromatography on silica gel.

Completion of the synthesis was achieved by in situ amine debenzylation and reductive cyclization of the resulting aminoketones. Thus, dibenzylaminoketones **11a** and **11b** were subjected to catalytic hydrogenation in the presence of 20% $Pd(OH)_2$/C. (+)-Deoxocassine (**1**)[15] and its C-6 ethyl analogue **10** were specifically obtained in 75 and 61% yield, respectively, after purification by chromatography on silica gel in a two-step sequence. A high degree of stereocontrol was observed, as Δ^1-piperidine intermediate **23** was hydrogenated from the less-hindered α-face of the molecule,[5e] resulting in the "all-*cis*" configuration. Not even a trace amount of the C-6 epimer could be detected in either case by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. The optical rotation of synthetic **1** {$[\alpha]_D$ = +11.6 (*c* = 0.95, $CHCl_3$)} was consistent with that reported for natural **1** {$[\alpha]_D$ = +11.8 (*c* = 1.0, $CHCl_3$)}.[5h] The ^{1}H NMR, ^{13}C NMR, and mass spectra and the melting point of synthetic **1** were also in good agreement with the reported values.[5h] Deoxocassine C-6 ethyl analogue **10**, which to the best of our knowledge has never been described, exhibited an optical rotation of $[\alpha]_D$ = +8.8 (*c* = 1.1, $CHCl_3$). It is interesting to note that the "all-*cis*" relationship between the substituents in **1** and **10** was confirmed by the small $J_{2,3}$ value (1.3 Hz), typical for the axial–equatorial H-2 and H-3 protons[5b,16] (Figure 2). Moreover, the *cis* relationship between the substituents at the 2,6-positions for compound **10** was confirmed by NOESY experiments (see the Supporting Information).

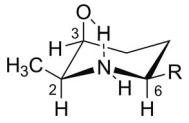


Figure 2. Major conformer of *cis*-2-methyl-6-substituted piperidin-3-ols.

Conclusions

In conclusion, we have achieved a flexible total synthesis of (+)-deoxocassine (**1**) and its C-6 ethyl analogue **10** by using a new, general, and efficient protocol. The approach involves the coupling of the aza-enolates of hydrazones **12a** and **12b** with oxirane **13** as a key reaction step. On the basis of previous reported syntheses, it is interesting to note that our route avoids the use of a protecting group for the 3-hydroxy function. The obvious synthetic potential of this short reaction sequence arises from its convergent nature. In this regard, this is a promising strategy that is attractive for the synthesis of other "all-*cis*" 2-methyl-6-substituted piperidine-3-ols alkaloids (for example, **2**–**7**) by using key intermediate **13** as a building block and by judicious choice of the ketone moiety. Extension of this methodology to the synthesis of other natural piperidine alkaloids is currently under investigation.

Experimental Section

Typical Procedure for the Synthesis of 11b: *n*BuLi (2.5 M in hexane, 0.4 mL, 1 mmol) was slowly added to a solution of hydrazone **12b** (255 mg, 1.00 mmol) in THF (2 mL) at 0 °C. The mixture was stirred at 0 °C for 1.5 h. The system was then warmed to room temperature and stirred for 10 min. A solution of epoxide **13** (48 mg, 0.179 mmol) in THF (5 mL) was added. The mixture was stirred for 6.5 h at room temperature and then quenched with saturated aqueous NH_4Cl (5 mL). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in THF (3 mL) and H_2O (3 mL) and SiO_2 (1 g) were added. The mixture was stirred overnight, filtered, and the phases were separated. The aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (cyclohexane/EtOAc, 99:1 to 95:5) to give **11b** as a white solid (72 mg, 79%). R_f = 0.29 (cyclohexane/EtOAc, 4:1). $[\alpha]_D$ = +21.2 (*c* = 0.85, $CHCl_3$). M.p. 39 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 10 H, CH_{arom}), 4.49 (br. s, 1 H, O*H*), 3.80 (d, *J* = 13.3 Hz, 2 H, NCH_aH$_b$Ph), 3.43 (td, *J* = 2.5, 9.2 Hz, 1 H, C*H*OH), 3.30 (d, *J* = 13.3 Hz, 2 H, NCH$_a$$H_b$Ph), 2.61–2.42 (m, 3 H, C*H*N, CH_2C=O), 2.39–2.26 (m, 2 H, CH_2C=O), 1.88–1.78 (m, 1 H, CH_aH$_b$CHOH), 1.53–1.50 (m, 2 H, CH_2CH$_2$C=O), 1.31–1.24 [m, 19 H, CH$_a$$H_b$CHOH, $(CH_2)_9$], 1.04 (d, *J* = 6.7 Hz, 3 H, 3 H, CH_3CHN), 0.88 (t, *J* = 6.9 Hz, 3 H, CH_3CH$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.5 (C=O), 138.9 (C_{arom}), 129.1 (CH_{arom}), 128.5 (CH_{arom}), 127.3 (CH_{arom}), 69.9 (CH), 58.3 (CH), 53.3 (CH_2), 43.0 (CH_2), 38.6 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.5 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 29.3 (CH_2), 27.4 (CH_2), 23.9 (CH_2), 22.7 (CH_2), 14.2 (CH_3), 8.0 (CH_3) ppm. MS (ESI): *m*/*z* = 480.5 $[M + H]^+$. HRMS: calcd. for $C_{32}H_{50}NO_2^+$ 480.3842; found 480.3840.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, characterization data of the new prepared compounds, and copies of the ^{1}H and ^{13}C NMR spectra.

Acknowledgments

Thanks are expressed to Mr. Pierre Sánchez for his help in mass spectrometry analysis and to Aurélien Lebrun for recording some NMR spectra. We thank the Ministère de l'Enseignement Supérieur et de la Recherche for providing a research grant for the PhD thesis project of P.Y.G.

[1] C. Viegas Jr., V. da S. Bolzani, M. Furlan, E. J. Barreiro, M. C. M. Young, D. Tomazela, M. N. Eberlin, *J. Nat. Prod.* **2004**, *67*, 908–910 and references cited therein.
[2] A. Numata, T. Ibuka in *The Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1987**, vol. 31, pp. 193–315.
[3] D. Lythgoe, M. J. Vernenge, *Tetrahedron Lett.* **1967**, *8*, 1133–1137.
[4] a) G. M. Strunz, J. A. Findlay in *The Alkaloids* (Ed.: A. Brossi), Academic Press, San Diego, **1986**, vol. 26, pp. 89–183; b) M. J. Schneider in *Alkaloids: Chemical and Biological Perspectives* (Ed.: S. W. Pelletier), Wiley, New York, **1996**, vol. 10, pp. 155–355.
[5] For examples of chiral pool approaches in the synthesis of "all-*cis*" 2-methyl-6-substituted piperidin-3-ol alkaloids, see: a) S. Hanessian, R. Frenette, *Tetrahedron Lett.* **1979**, *20*, 3391–3394;

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

b) K. Kurihara, T. Sugimoto, Y. Saitoh, Y. Igarashi, H. Hirota, Y. Moriyama, T. Tsuyuki, T. Takahashi, Q. Khuong-Huu, *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3337–3345; c) T. Kiguchi, M. Shirakawa, I. Ninomiya, T. Naito, *Chem. Pharm. Bull.* **1996**, *44*, 1282–1284; d) T. Kiguchi, M. Shirakawa, R. Honda, I. Ninomiya, T. Naito, *Tetrahedron* **1998**, *54*, 15589–15606; e) K. K. Kumar, A. Datta, *Tetrahedron* **1999**, *55*, 13899–13906; f) C. Herdeis, T. Schiffer, *Tetrahedron* **1999**, *55*, 1043–1056; g) H. K. Lee, J. S. Chun, C. S. Pak, *Tetrahedron* **2003**, *59*, 6445–6454; h) J. M. Andrés, R. Pedrosa, A. Pérez-Encabo, *Eur. J. Org. Chem.* **2007**, 1803–1810.

[6] For examples of asymmetric synthesis of "all-*cis*" 2-methyl-6-substituted piperidin-3-ol alkaloids, see: a) T. Momose, N. Toyooka, *Tetrahedron Lett.* **1993**, *34*, 5785–5786; b) N. Toyooka, Y. Yoshida, T. Momose, *Tetrahedron Lett.* **1995**, *36*, 3715–3718; c) J. Oetting, J. Holzkamp, H. H. Meyer, A. Pahl, *Tetrahedron: Asymmetry* **1997**, *8*, 477–484; d) T. Momose, N. Toyooka, M. Jin, *J. Chem. Soc. Perkin Trans. 1* **1997**, 2005–2013; e) D. Enders, J. H. Kirchhoff, *Synthesis* **2000**, 2099–2105; f) D. Ma, N. Ma, *Tetrahedron Lett.* **2003**, *44*, 3963–3965; g) S. R. V. Kandula, P. Kumar, *Tetrahedron* **2006**, *62*, 9942–9948; h) C. A. Leverett, M. P. Cassidy, A. Padwa, *J. Org. Chem.* **2006**, *71*, 8591–8601; i) G. Kim, N. Kim, *Tetrahedron Lett.* **2007**, *48*, 4481–4483; j) R. Noël, C. Vanucci-Bacqué, M.-C. Fargeau-Bellassoued, G. Lhommet, *Eur. J. Org. Chem.* **2007**, 476–486; k) S. Raghavan, S. Mustafa, *Tetrahedron* **2008**, *64*, 10055–10061.

[7] A synthesis of spectaline (**4**) by opening of an epoxide has already been reported: B. M. Trost, Z. T. Ball, K. M. Laemmerhold, *J. Am. Chem. Soc.* **2005**, *127*, 10028–10038.

[8] P.-Y. Géant, J. Martínez, X. J. Salom-Roig, *Eur. J. Org. Chem.* **2011**, 1300–1309.

[9] We have improved the yields of this two-step sequence by using crude **17** without purification (see ref.[8]).

[10] C. Tenca, A. Dossena, R. Marchelli, G. Casnati, *Synthesis* **1981**, 141–142.

[11] For this last two-step sequence, yields could be improved by removing methyl *p*-tolyl sulfide under vacuum before purification of oxirane **13** by column chromatography on silica gel. For examples in the synthesis of epoxides by sulfonium salt elimination, see: C. H. Behrens, K. B. Sharpless, *Aldrichim. Acta* **1983**, *16*, 67–79.

[12] R. Lazny, A. Nodzewska, *Chem. Rev.* **2010**, *110*, 1386–1434.

[13] For examples of hydrazone alkylation by oxiranes, see: a) D. A. Evans, S. L. Bender, J. Morris, *J. Am. Chem. Soc.* **1988**, *110*, 2506–2526; b) T. Nishiyama, J. F. Woodhall, E. N. Lawson, W. Kitching, *J. Org. Chem.* **1989**, *54*, 2183–2189; c) D. F. Taber, Y. Song, *J. Org. Chem.* **1997**, *62*, 6603–6607; d) D. Enders, I. Breuer, A. Nühring, *Eur. J. Org. Chem.* **2005**, 2677–2683.

[14] A. G. Myers, A. L. McKinstry, *J. Org. Chem.* **1996**, *61*, 2428–2440.

[15] For other syntheses of (+)- and (–)-deoxocassine described in the literature, see ref.[5b,5h,6f–6h,6j,6k]

[16] M. Paterne, R. Dhal, E. Brown, *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1321–1324.

Received: September 12, 2011
Published Online: November 17, 2011

 © 2012 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim