# From a Biogenetic Scenario to a Synthesis of the ABC Ring of Manzamine A

Matthias Herdemann, Ali Al-Mourabit, Marie-Thérèse Martin, and Christian Marazano*

*Institut de Chimie des Substances Naturelles, CNRS, 91198 Gif-sur-Yvette, France*

*marazano@icsn.cnrs-gif.fr*

*Received October 16, 2001*

On the basis of a biogenetic proposal for explaining the biogenesis of manzamine A, the cycloaddition of dihydropyridinium salt **26** with diene derivative **5** leads to adducts **27**. These adducts, as well as their related and previously described analogues **9**, are now shown to be precursors of diene derivatives such as **10**, **13**, and **28**. Treatment of diene **32** with sodium azide resulted in a one-step formation of the tricyclic imino derivative **34**. This key intermediate was further transformed into tricyclic derivative **40**, which possesses the essential features of the ABC ring of manzamine A.

## Introduction

Since its isolation in 1986,[1] the cytotoxic marine sponge alkaloid manzamine A (Scheme 1) has been the subject of many synthetic efforts,[2] resulting in particular in two total syntheses.[3] Interest for this natural product and its analogues has been renewed recently with the discovery of their potent activities against infectious diseases.[4] The process by which manzamine A is biosynthesized remains unknown, as it is for the numerous other related alkaloids isolated from sponges in the same order (*Haplosclerida*).[5] Nevertheless, the biosyntheses of these alkaloids are likely to result from the condensation of a three-carbon unit and long-chain aldehydes with ammonia. This process is completed, in some cases, by the addition of an amino acid derivative (tryptamine for manzamine A). A hypothetical biogenetic route, starting from such species, was initially proposed by Baldwin and Whitehead.[6] This hypothesis, which focused on the chemistry of dihydropyridine intermediates, has been tested experimentally.[7] While encouraging results were obtained in testing this model (synthesis of keramaphidin B albeit in low yield),[7b] the chemistry involved was limited by competitive oxido-reduction reactions of unstable dihydropyridine intermediates. An alternative model[8] avoiding such inconvenience, depicted in Scheme 1, would involve cycloaddition of an intermediate **1** to give, after reduction, the key compound **2**, initially proposed[2] as a precursor of manzamine A. This model has the advantage of implicating an aminopentadienal function that could also be a likely intermediate in the biosynthesis of natural pyridinium salts also isolated from sponges of the *Haplosclerida* order.[8b] A reaction that mimics the transformation of the intermediate **1**, to give adduct **2**, was recently reported (see Scheme 2).[8a] In this paper, a short synthesis of the ABC ring of manzamine A based upon this approach is now presented.

## Results and Discussion

The initially reported reaction[8a] that mimics the key transformation of intermediate **1** to give adduct **2** is depicted in Scheme 2. Treatment of tetrahydropyridine **3** with camphorsulfonic acid (CSAH) gave dihydropyridinium salt **4**, condensation of which with aminopentadiene **5** proceeded smoothly. A cycloaddition reaction occurred that is probably stepwise, giving first adduct **6**, followed by cyclization to give iminium ion **7**. The overall process is potentially reversible, but an intramolecular oxido-reduction of intermediate **7** irreversibly gave imine **8**, which was not isolated but hydrolyzed to give the cycloadducts **9** (two diastereoisomers).

Among the numerous related cycloaddition strategies that have been used for construction of the central AB rings of manzamine A, this approach is certainly one of the most efficient since it brings together all the important functionalities in a single step. But the problem associated with this approach is the opposite relative stereochemistry of the exocyclic nitrogen in adduct **9** when compared to that of the natural alkaloid (compare with structure **2** in Scheme 1).

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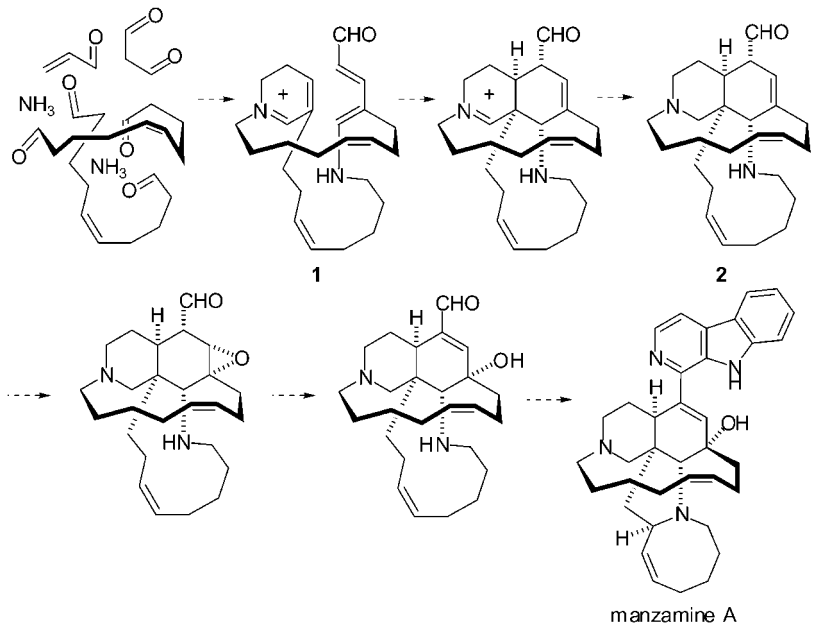
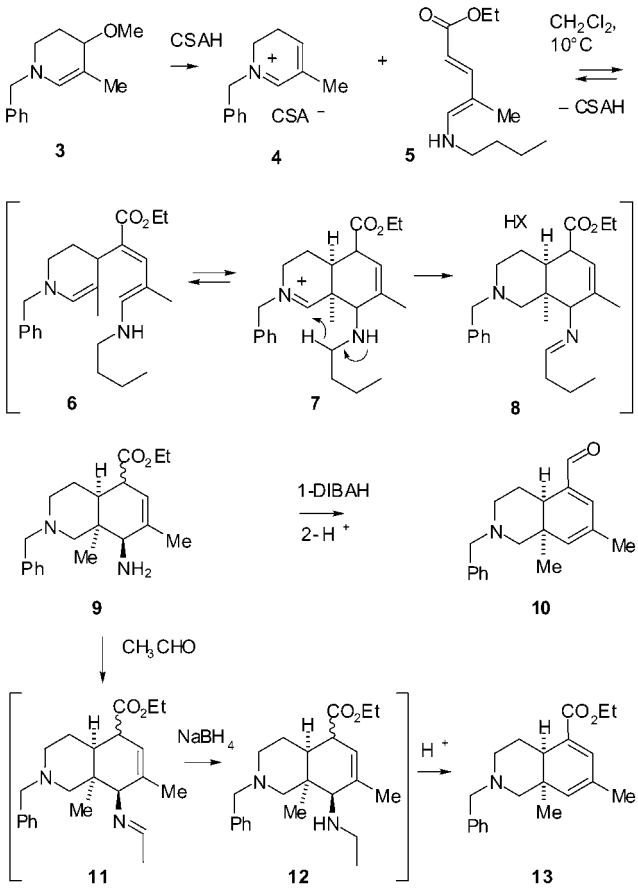
10.1021/jo0162033 CCC: $22.00 
Published on Web 02/21/2002

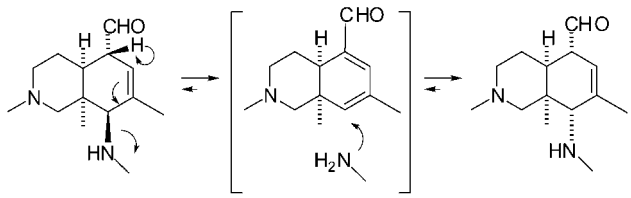
**Scheme 1**



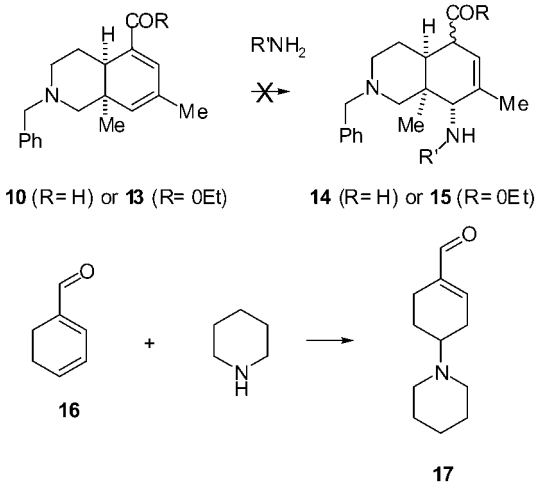

**Scheme 2**



**Scheme 3**



**Scheme 4**

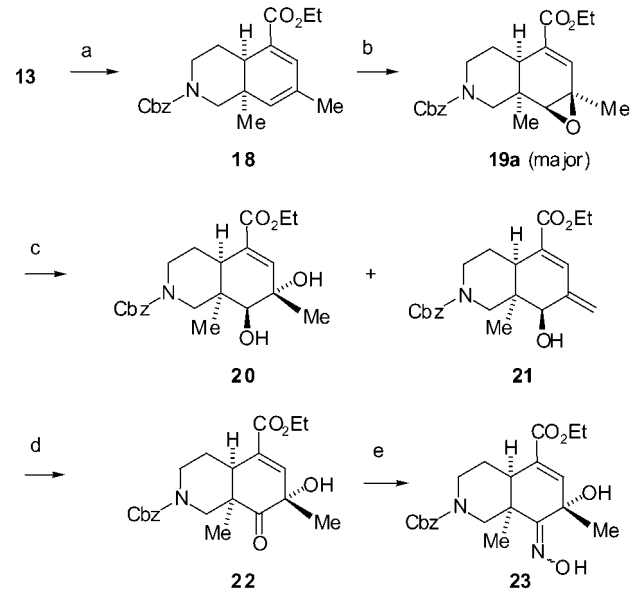


As reported here, this nitrogen functionality is in fact very sensitive to elimination. Thus, treatment of the crude mixture of isomers **9** with DIBAH gave only diene–aldehyde **10**, which was recovered, without isolation of any intermediate, in 27% overall yield from tetrahydropyridine **3**. The amino group in esters **9** was more resistant to elimination, but the corresponding secondary amine (**12**) was again easily eliminated under acidic conditions to give diene **13** in 38% overall yield from tetrahydropyridine **3**. These results were in favor of our initial proposal[8a] suggesting that the secondary nitrogen functionality can be in equilibrium via an elimination–addition process (Scheme 3) in the hypothetic intermediate **2**.

Unfortunately, in our hands, the related nucleophilic addition of a primary amine onto derivatives **10** or **13** failed to give the corresponding adducts **14** or **15**, respectively (Scheme 4), though we observed that piperidine added smoothly at ambient temperature on model diene **16** to give only adduct **17** (69% isolated yield with 85% conversion).

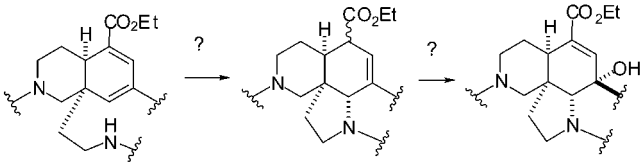
Due to this failure, the introduction of the secondary nitrogen, after oxidation of the diene function, was then

**Scheme 5**[a]




[a] Key: (a) $PhCH_2OCOCl$, $CH_2Cl_2$, 20 °C, 20 h (98% yield); (b) *m*-CPBA, $CH_2Cl_2$, 40 h (80% yield, 70% de); (c) *p*-TsOH, acetone $H_2O$, 20 h (73% yield for **20**, 16% for **21**); (d) PCC, $CH_2Cl_2$, 40 h (88% yield); (e) $NH_2OH$,HCl, $C_5H_5N$, 100 °C, 4 days (71% yield).

**Scheme 6**



considered. Epoxidation reactions on diene **13** were thus investigated (Scheme 5). For this purpose, the protecting benzyl group was first exchanged by treatment with benzyl chloroformate to give carbamate **18**. Epoxidation of this derivative with *m*-CPBA proceeded with complete regioselectivity to give two diastereoisomeric epoxides **19a** ($\beta$ epoxide) and **19b** ($\alpha$ epoxide) in a 85:15 ratio. The major isomer **19a**[9] was isolated by chromatography on silica gel and was recovered in 80% yield. Ring opening of this epoxide in acidic medium was again regioselective, affording diol **20** in 73% yield. The only byproduct of the reaction was the dehydrated derivative **21**. Oxidation of diol **20** with PCC finally gave derivative **22** in good yield. The keto function of **22** was found to be unreactive toward primary amines and no imine was obtained, even under forcing conditions. While the oxime **23** could be obtained in good yield, its reduction to a primary amine also failed. Introduction of an amino group via a ketone is probably difficult for steric reasons. Though unsuccessful, we believe that the results depicted in Scheme 5 can be of some informative value concerning the reactivity of dienes such as **18**.

A likely alternative involving the intramolecular version of amine addition depicted in Scheme 6, was then considered. This strategy led to a successful synthesis of the ABC ring of manzamine A as now reported.

Starting from the commercially available pyridine derivative **24** (Scheme 7), standard procedures led to tetrahydropyridine **25** in 50% overall yield. The corresponding dihydropyridinium salt **26**[10] was then condensed with diene **5**. Treatment of the resulting crude adduct **27** using the conditions employed for preparation of diene **13** afforded diene **28,** which was isolated in 28% yield from tetrahydropyridine **25**. Further introduction of an amine function turned out to be difficult since attempts to activate the hydroxyl group, to allow displacement by an azide group, invariably led to the quaternary ammonium salt **30**.

To avoid this, the corresponding carbamate **31** was used as starting material (Scheme 8). This product was easily obtained, though a temporary protection of the hydroxyl group was found to be necessary. Treatment of the corresponding mesylate **32** with sodium azide in DMF gave a mixture of isomeric derivatives **33** and **34** in approximately 3:2 ratio. A plausible mechanism, explaining this remarkable consecutive reaction sequence, was easily deduced from a comparison with related results previously reported by Hudlicky et al.[11] Thus, the azido group of unstable intermediate **35** may first add to the diene function, giving the triazole derivative **36**, a process that would be followed by spontaneous nitrogen elimination producing aziridine **37**. Analysis of a model (Scheme 9) reveals that aziridine **37** is perfectly oriented for a ring opening associated with hydrogen transfer.

This process is expected to selectively deliver tricyclic imine **33**, but the ester group probably epimerizes under the reaction conditions to give the mixture of esters **33** and **34**.

Sodium borohydride reduction of esters **33** and **34** afforded isomeric amines **38a** and **38b** respectively (Scheme 10). These compounds were selectively oxidized to epoxides **39a** and **39b** using previously reported conditions.[12] These epoxides were too unstable to be isolated, but treatment of each epoxide with base finally gave the same alcohol **40**.[13] The reaction sequence has also been applied to the crude mixture of imino derivatives **33** and **34** without isolation of any intermediate. In this case, the amino alcohol **40** was obtained in a comparable and reproducible overall yield of about 70%. The stereochemistry of this key derivative **40**, which possesses the essential features of the ABC ring of manzamine A, was secured by the observation that this product formed the oxazolidine **41** in the presence of formaldehyde.

## Conclusion

Using the strategy based on the biogenetic considerations depicted in Scheme 1, it is now possible to obtain derivatives such as **40** that possess several essential features of the manzamine A skeleton. Derivative **40** was obtained in eight steps and in 16% overall yield from diene **5** and readily available tetrahydropyridine **25**. A total synthesis of manzamine A is conceivable using this approach, but intermediates such as **40** are also to be

(9) All complex structures were resolved by intensive NMR-spectroscopy studies including 1D and 2D NMR experiments (COSY 90, NOESY, HMQC, HMBC). Information concerning details of NOE effects in three key structures (**20**, **33**,and **41**) are given as Supporting Information.

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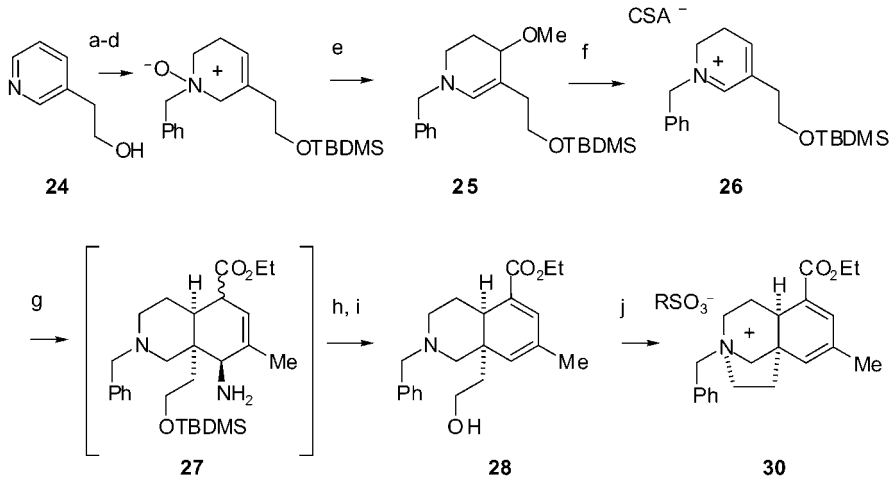
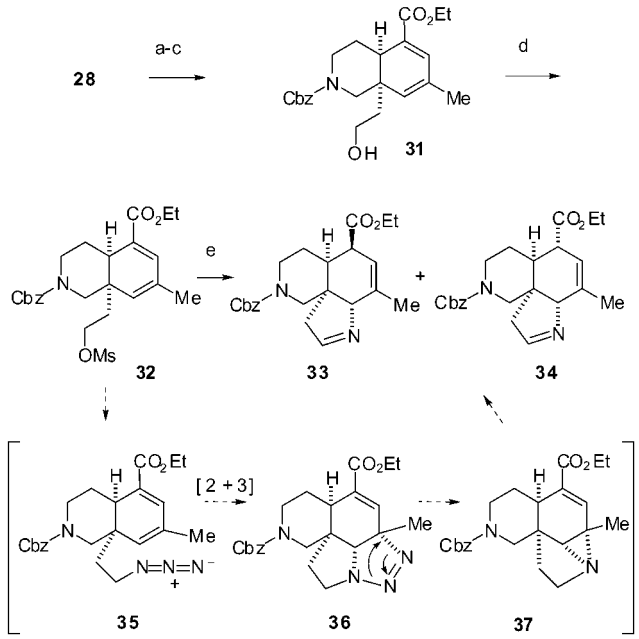
(13) The observed selectivity is likely to be due to the orientation of the peracid attack by the protons of the intermediate trifluoroacetic salt of the secondary amine. For a discussion of this effect, see ref 12.

**Scheme 7**[a]



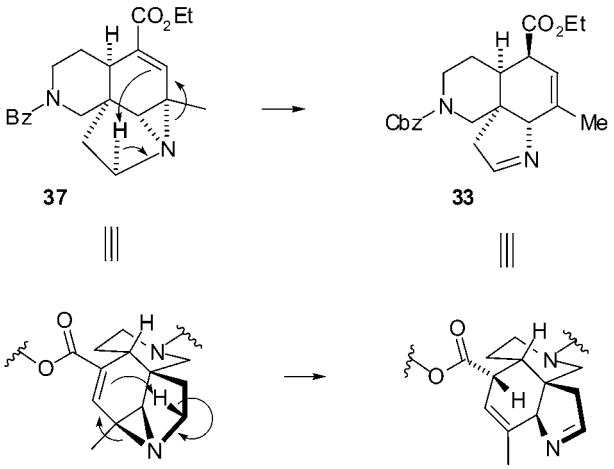

[a] Key: (a) TBDMSCl, DMF, imidazole, 20 °C, 15 h (97% yield); (b) BnBr, toluene 65 °C, 40 h (90% yield); (c) $NABH_4$, MeOH (80% yield); (d) *m*-CPBA, $CH_2Cl_2$, (99% yield); (e) TFAA, $CH_2Cl_2$, (then MeONa, MeOH (69% yield); (f) CSAH, $CH_2Cl_2$; (g) diene **5** (1 equiv), 4 °C, 15 h; (h) $CH_3CHO$, $Al_2O_3$, $CH_2Cl_2$, (i) $NaBH_4$, MeOH, then $HCl-H_2O$ (diene **28:** 28% overall yield from **25**); (j) MsCl, $NEt_3$, $CH_2Cl_2$ or TsCl, $C_5H_5N$.

**Scheme 8**[a]




[a] Key: (a) TBDMSCl, DMF, imidazole; (b) $PhCH_2OCOCl$,$CH_2Cl_2$, 20 °C, 4 days; (c) TBAF, THF 2 h; (d) MsCl, $CH_2Cl_2$, $NEt_3$, 1 h (85% overall yield from **30**); (e) $NaN_3$, DMF, 60 °C, 24 h (approximate ratio for 33/34: 3/2, 67% combined yield).

**Scheme 9**



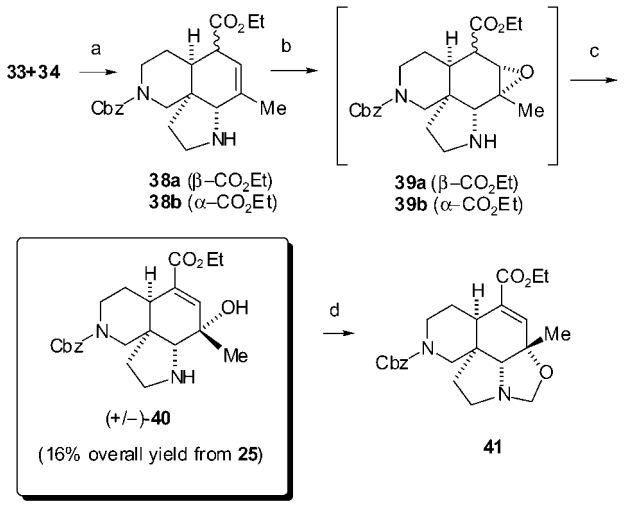

considered as well suited for the preparation of analogues of this biologically interesting family of alkaloids.

## Experimental Section

**2-Benzyl-7,8a-dimethyl-1,2,3,4,4a,8a-hexahydroisoquinoline-5-carbaldehyde (10).** Tetrahydropyridine **3** (513 mg, 2.36 mmol) was treated successively with camphorsulfonic acid (685 mg, 2.95 mmol) and diene **5** (623 mg, 2.95 mmol) using the conditions previously reported.[8a] The crude resulting mixture of esters **9** was dissolved in $Et_2O$ (90 mL), and a solution of DIBAH in toluene (1 M, 10 mL) was added, at −78 °C, under nitrogen. After 0.5 h of stirring, $H_2O$ (1 mL) was added and stirring was continued during 1 h at ambient temperature. The reaction mixture was filtered over Celite. Removal of solvents under reduced pressure left an oil that was chromatographed over silica gel (heptane/AcOEt 95/5, 0.1% $NEt_3$). Aldehyde **10** (180 mg, 0.64 mmol, 27% overall yield from **3**) was isolated as a colorless oil that crystallized upon standing: mp = 62 °C; IR ($CHCl_3$) 3019, 2921, 2808, 1667, 1216 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.70 (s, 3H), 1.32 (ddd, $J$ = 4.2, 12.5, 16.7 Hz, 1H), 1.56−1.64 (m, 1H), 1.73 (d, $J$ = 11.6 Hz, 1H), 1.86−1.95 (m, 1H), 1.91 (d, $J$ = 1.5 Hz, 3H), 2.36 (dd, $J$ = 3.7, 12.5 Hz, 1H), 2.67 (dd, $J$ = 1.8, 11.6 Hz, 1H), 2.76−2.84 (m, 1H), 3.36 (d, $J$ = 13.4 Hz, 1H), 3.66 (d, $J$ = 13.4 Hz, 1H), 5.76 (dd, $J$ = 1.3, 1.5 Hz, 1H), 6.59 (d, $J$ = 1.0 Hz, 1H), 7.27−7.38 (m, 5H), 9.53 (s, 1H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 20.6, 23.3, 27.4, 36.3, 36.7, 52.7, 63.3, 63.8, 127.0, 128.2 (2C), 129.0 (2C), 129.3, 138.4, 141.3, 142.0, 144.6, 192.8; MS ($ES^+$) $m/z$ 282 ($MH^+$, 100).

**2-Benzyl-7,8a-dimethyl-1,2,3,4,4a,8a-hexahydroisoquinoline-5-carboxylic Acid Ethyl Ester (13).** Tetrahydropyridine **3** (551 mg, 2.53 mmol) was treated successively with camphorsulfonic acid (735 mg, 3.16 mmol) and diene **5** (560 mg, 2.64 mmol) under the conditions previously reported.[8a] To the resulting crude mixture of esters **9**, dissolved in $CH_2Cl_2$ (50 mL), were added alumina (2 g) and acetaldehyde (1 mL, 17.7 mmol). The resulting solution was stirred at ambient temperature during 15 h and filtered, and the solvent was evaporated. Reduction was then performed at 20 °C in MeOH, using an $NaBH_4$ excess, during 1 h. $H_2O$ was added to the reaction mixture, which was acidified with aqueous HCl (pH < 1). After neutralization with an excess of a saturated $NaHCO_3$ aqueous solution, the products were extracted with

**Scheme 10**[a]




[a] Key: (a) $NaBH_4$, MeOH (88% yield); (b) (i) TFA, $CH_2Cl_2$, (ii) $CF_3CO_3H$, $CH_2Cl_2$ 0 °C, 45 min, (iii) $Na_2SO_3$, (iv) $NaHCO_2$; (c) NaOEt, EtOH 80% overall yield from **38a**,**b**); (d) HCNO, $CH_3CN$, AcOH, 15 h (91% yield).

$CH_2Cl_2$. Removal of solvents under reduced pressure left a residue which was chromatographed over silica gel (heptane/AcOEt 95/5, 0.1% $NEt_3$). Diene **13** was isolated as a pale yellow oil (314 mg, 0.97 mmol, 38% yield from **3**): IR (film) 3027, 2919, 2801, 2763, 1704, 1579, 1453, 1268, 1215 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.72 (s, 3H), 1.29 (t, $J$ = 7.1 Hz, 3H), 1.36 (ddd, $J$ = 4.1, 12.2, 13.2 Hz, 1H), 1.59−1.68 (m, 1H), 1.75 (d, $J$ = 11.4 Hz, 1H), 1.80−1.90 (m, 1H), 1.83 (d, $J$ = 1.5 Hz, 3H), 2.25 (ddd, $J$ = 1.1, 4.6, 12.2 Hz, 1H), 2.68, (dd, $J$ = 1.8, 11.4 Hz, 1H), 2.75−2.82 (m, 1H), 3.38 (d, $J$ = 13.0 Hz, 1H), 3.59 (d, $J$ = 13.0 Hz, 1H), 4.20 (q, $J$ = 7.1 Hz, 2H), 5.54 (dd, $J$ = 1.2, 1.5 Hz, 1H), 6.84 (d, $J$ = 1.2 Hz, 1H), 7.20−7.36 (m, 5H); $^{13}C$ NMR ($CD_3OD$, 75 MHz) $\delta$ 14.6, 20.9, 23.8, 28.6, 37.7, 40.4, 53.7, 61.6, 64.2, 65.0, 128.2, 129.2 (2C), 130.4 (2C), 132.2, 136.0, 139.0, 139.3, 168.7; SM (EI) $m/z$ 325 ($M^{\bullet+}$, 33), 146 ($C_{10}H_{12}N^+$, 100), 134 ($C_9H_{12}N^+$, 56), 104 ($C_7H_6N^+$, 61), 91 ($C_7H_7$+, 72); SM (CI, isobutane) $m/z$ 326 ($MH^+$, 39), 146 ($C_{10}H_{12}N^+$, 100), 134 ($C_9H_{12}N^+$, 29), 91 ($C_7H_7^+$, 72); HRMS (CI, isobutane) calcd for $C_{21}H_{28}NO_2$ ($MH^+$) 326.2163, found 326.2159.

**7,8a-Dimethyl-3,4,4a,8a-tetrahydro-1*H*-isoquinoline-2,5-dicarboxylic Acid 2-Benzyl Ester 5-Ethyl Ester (18).** To a solution of diene **13** (92 mg, 0.28 mmol), in $CH_2Cl_2$ (10 mL), was added benzyl chloroformate (0.47 mL, 2.83 mmol), and the resulting mixture was stirred at ambient temperature during 20 h. After addition of a saturated aqueous solution of $NaHCO_3$, the reaction product was extracted with $CH_2Cl_2$. Removal of solvent under reduced pressure left a gum that was chromatographed over silica gel (heptane/AcOEt: gradient from 95/5 to 90/10). Carbamate **18** was obtained as a white powder (103 mg, 0.28 mmol, 98% yield): mp = 72 °C; IR (film) 3023, 2921, 2863, 1707, 1433, 1267, 1228, 1076 $cm^{-1}$; $^1H$ NMR (two rotamers, $CDCl_3$, 250 MHz) $\delta$ 0.82 (s, 3H), 1.20−1.35 (m, 1H), 1.32 (t, $J$ = 7.1 Hz, 3H), 1.58−1.70 (m, 1H), 1.76 and 1.79 (bs, 3H), 2.43 (dd, $J$ = 4.3, 11.4 Hz, 1H), 2.50−2.83 (m, 2H), 3.98−4.27 (m, 2H), 4.23 (q, $J$ = 7.1 Hz, 2H), 5.08−5.33 (m, 2H), 5.51 and 5.68 (bs, 1H), 6.84 (s, 1H), 7.26−7.42 (m, 5H); $^{13}C$ NMR (two rotamers, $CDCl_3$, 63 MHz) $\delta$ 14.3, 20.8, 22.5, 26.7, 37.3, 39.2, 43.7, 53.4, 60.5, 67.0, 127.9, 128.0 (2C), 0128.5 (2C), 130.6, 131.2, 134.8, 135.3 and 135.9, 137.0, 155.3, 167.0; SM (EI) $m/z$ (rel intensity) 369 ($M^{\bullet+}$, 27), 234 ($C_{14}H_{20}NO_2^+$, 88), 204 ($C_{12}H_{14}NO_2^+$, 95), 188 ($C_{12}H_{14}NO^+$, 100), 134 ($C_9H_{12}N^+$, 79), 91 ($C_7H_7^+$, 96); HRMS (CI, isobutane) calcd for $C_{21}H_{28}NO_2$ ($MH^+$) 370.2018, found 370.1999.

**1a,7a-Dimethyl-1a,4,7,7a,7b-hexahydro-3a*H*-1-oxa-6-azacyclopropa[*a*]naphthalene-3,6-dicarboxylic Acid 6-Benzyl Ester 3-Ethyl Ester (19a).** Diene **18** (167 mg, 0.452 mmol) was dissolved in $CH_2Cl_2$ (15 mL), *m*-CPBA (150 mg, 0.78 mmol) was added, and the resulting solution was stirred at ambient temperature during 40 h. After cooling at 0 °C, the reaction mixture was treated with a saturated aqueous solution of $Na_2SO_3$, The organic phase was collected. Removal of solvent under reduced pressure left a gum that was chromatographed over silica gel (heptane/AcOEt 80/20). The major epoxide **19a** (139 mg, 0.36 mmol, 80% yield) was isolated as a colorless oil: IR (film) 3032, 2969, 2931, 2870, 1707, 1442, 1274, 1207 $cm^{-1}$; $^1H$ NMR (two rotamers, $CDCl_3$, 300 MHz) $\delta$ 0.80 and 0.86 (s, 3H), 1.31 (t, $J$ = 7.2 Hz, 3H), 1.46 and 1.50 (s, 3H), 1.60−1.72 (m, 1H), 1.79 (m, 1H), 2.48−2.55 (m, 1H), 2.72−2.90 (m, 2H), 2.93 and 3.16 (s, 1H), 4.08−4.18 (m, 1H), 4.21 (q, $J$ = 7.2 Hz, 2H), 4.41 (d, $J$ = 13.6 Hz, 1H), 5.11 (d, $J$ = 12.4 Hz, 1H), 5.22 (d, $J$ = 12.4 Hz, 1H), 6.91 (bs, 1H), 7.28−7.40 (m, 5H); $^{13}C$ NMR (two rotamers, $CDCl_3$, 63 MHz) $\delta$ 14.2, 21.1, 21.7, 30.6 and 31.1, 34.2, 40.9, 44.7, 51.7, 52.9 and 53.1, 61.0, 67.1, 70.5, 127.9 (2C), 128.1 and 128.4 (2C), 135.6 and 137.0, 137.6 and 137.9, 155.2 and 155.4, 166.0; MS (EI) $m/z$ (rel intensity) 385 ($M^{\bullet+}$, 16), 367 ($M^{\bullet+} - H_2O$, 16), 342 ($M^{\bullet+} - C_2H_3O$, 29), 294 ($M^{\bullet+} - C_7H_7$, 29), 250 ($C_{14}H_{20}NO_3^+$, 97), 91 ($C_7H_7^+$, 100); HRMS (CI, isobutane) calcd for $C_{22}H_{28}NO_5$ ($MH^+$) 386.1968, found 386.1991. Pure minor epoxide **19b** was isolated as an oil (25 mg, 0.06 mmol, 14% yield): IR (film) 3033, 2981, 1712, 1433, 1266, 1169, 1089, 982 $cm^{-1}$; $^1H$ NMR (two rotamers, $CDCl_3$, 300 MHz) $\delta$ 0.88 (s, 3H), 1.30 (t, $J$ = 7.1 Hz, 3H), 1.34−1.45 (m, 1H), 1.41 (s, 3H), 1.77−1.90 (m, 1H), 2.28 (dd, $J$ = 4.3, 10.6 Hz, 1H), 2.89−3.16 (m, 2H), 2.91 (d, $J$ = 13.5 Hz, 1H), 3.83−4.09 (m, 1H), 4.07 (d, $J$ = 13.5 Hz, 1H), 4.21 (q, $J$ = 7.1 Hz, 2H), 5.16 (bs, 2H), 6.75 (s, 1H), 7.28−7.40 (m, 5H); $^{13}C$ NMR (two rotamers, $CDCl_3$, 75 MHz) $\delta$ 14.2, 20.7, 21.3, 30.6, 35.2, 40.3, 43.8, 53.3, 53.5, 61.0, 63.4, 67.3, 128.1, 128.2 (2C), 128.6 (2C), 135.7, 136.7, 138.0, 155.4, 166.3; MS (EI) $m/z$ (rel intensity) 385 ($M^{\bullet+}$, 18), 294 ($M^{\bullet+} - C_7H_7$, 87), 250 ($C_{14}H_{20}NO_3^+$, 100), 204 ($C_{12}H_{14}NO_2^+$, 70), 140 (99), 91 ($C_7H_7^+$, 98); MS (CI, isobutane) $m/z$ (rel intensity) 386 ($MH^+$, 100), 342 ([$M - C_2H_3O$]$^+$, 70), 250 ($C_{14}H_{20}NO_3^+$, 60), 91 ($C_7H_7^+$, 98).

**7,8-Dihydroxy-7,8a-dimethyl-3,4,4a,7,8,8a-hexahydro-1*H*-isoquinoline-2,5-dicarboxylic Acid 2-Benzyl Ester 5-Ethyl Ester (20).** To major epoxide **19a** (230 mg, 0.6 mmol), in acetone (5 mL) and $H_2O$ (15 mL), was added, under vigorous stirring, *p*-toluenesulfonique acid monohydrate (114 mg, 0.6 mmol). The resulting mixture was stirred at ambient temperature during 20 h and then treated with a saturated aqueous $NaHCO_3$ solution. Extraction with $CH_2Cl_2$ and removal of solvent under reduced pressure gave a mixture that was chromatographed over silica gel (heptane/AcOEt/MeOH: gradient from 80/20/0 to 60/40/1) to give pure diol **20** (176 mg, 0.44 mmol, 73% yield) as major product: IR (film) 3445, 2932, 1682, 1446, 1253, 1098 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.01 (s, 3H), 1.31 (t, $J$ = 7.0 Hz, 3H), 1.38 (s, 3H), 1.70−1.90 (m, 2H), 1.95 (s, 1H), 2.44 (dd, $J$ = 5.3, 10.7 Hz, 1H), 2.78 (bs, 1H), 2.97 (d, $J$ = 14.0 Hz, 1H), 3.03 (ddd, $J$ = 3.7, 11.2, 13.4 Hz, 1H), 3.66 (d, $J$ = 3.0 Hz, 1H), 3.97 (m, 1H), 4.11 (d, $J$ = 14.0 Hz, 1H), 4.16−4.30 (m, 2H), 5.10 (d, $J$ = 12.4 Hz, 1H), 5.17 (d, $J$ = 12.4 Hz, 1H), 6.68 (s, 1H), 7.28−7.40 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.3, 25.0, 26.2, 28.1, 36.0, 40.1, 44.1, 52.9, 60.9, 67.3, 71.9, 82.0, 127.9 (2C), 128.1(2C), 128.6 (2C), 132.2, 136.8, 140.2, 156.0, 167.1; MS (CI, isobutane) $m/z$ (rel intensity) 404 ($MH^+$, 100), 386 ($MH^+ - H_2O$, 44), 360 (54), 342 (56), 268 (64), 252 (55), 250 ($C_{14}H_{20}NO_3^+$, 47), 91 ($C_7H_7^+$, 37); HRMS (CI, isobutane) calcd for $C_{22}H_{30}NO_6$ ($MH^+$) 404.2073, found 404.2066. Dehydrated product **21** was also isolated as a minor product (37 mg, 0.096 mmol, 16% yield): IR (film) 3450, 3033, 2930, 1702, 1439, 1244 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 250 MHz) $\delta$ 0.75 (s, 3H), 1.32 (t, $J$ = 7.1 Hz, 3H), 1.77−2.05 (m, 2H), 2.40 (bs, 1H), 2.50 (dd, $J$ = 5.3, 10.5 Hz, 1H), 2.97 (d, $J$ = 14.1 Hz, 1H), 3.06 (m, 1H), 3.98−4.18 (m, 3H), 4.24 (q, $J$ = 7.1 Hz, 2H), 5.14 (s, 2H), 5.44 (s, 2H), 7.19 (s, 1H), 7.25−7.40 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 63 MHz) $\delta$ 14.4, 23.7, 27.7, 35.9, 40.6, 44.3, 52.8, 60.8, 67.2, 78.0, 122.7, 127.9 (2C), 128.0 (2C), 128.6 (2C), 132.0, 134.6, 137.0, 143.8, 156.0, 167.0; MS ($ES^+$) $m/z$ 809.1 ($2M + K^+$, 100), 793.1 ($2M + Na^+$, 65), 424.0 ($MK^+$, 34), 408.0 ($MNa^+$, 100); HRMS (CI, isobutane) calcd for $C_{22}H_{28}NO_5$ ($MH^+$) 386.1967, found 386.1956.

**7-Hydroxy-7,8a-dimethyl-8-oxo-3,4,4a,7,8,8a-hexahydro-1*H*-isoquinoline-2,5-dicarboxylic Acid 2-Benzyl Ester 5-Ethyl Ester (22).** To a solution of diol **20** (198 mg, 0.49 mmol) in $CH_2Cl_2$ (15 mL) was added, at 0 °C and under vigorous stirring, PCC (264 mg, 1.22 mmol). After 40 h at ambient temperature, $Et_2O$ (40 mL) was added, and the resulting mixture was filtered. Evaporation of solvents under reduced pressure left a gum that was chromatographed over silica gel (heptane/AcOEt 80/20). Pure ketone **22** (173 mg, 0.45 mmol, 88% yield) was isolated as a colorless oil: IR (film) 3418, 2980, 2930, 1710, 1435, 1272, 1220 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 0.91−1.11 (m, 1H), 1.15 (s, 3H), 1.35 (t, $J$ = 7.0 Hz, 3H), 1.41 (s, 3H), 2.02 (bd, $J$ = 12.5 Hz, 1H), 2.53 (bd, $J$ = 13.2 Hz, 1H), 2.70 (s, 1H), 2.70−2.84 (m, 1H), 2.87 (dd, $J$ = 3.9, 12.6 Hz, 1H), 4.07−4.35 (m, 3H), 4.90 (bd, $J$ = 13.2 Hz, 1H), 5.30 (bs, 2H), 6.96 (s, 1H), 7.27−7.52 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.3, 23.3, 26.6, 31.9, 42.8, 43.6, 46.6, 48.6, 61.4, 67.3, 69.9, 127.8, 127.9 (2C), 128.5 (2C), 132.3, 136.9, 140.5, 155.1, 165.9, 212.8; SM (IC, isobutane) *m/z* (rel intensity) 402 ($MH^+$, 80), 340 (78), 324 (35), 250 ($C_{14}H_{20}NO_3^+$, 42), 91 ($C_7H_7^+$, 100).; HRMS (CI, isobutane) calcd for $C_{22}H_{28}NO_6$ ($MH^+$) 402.1917, found 402.1935.

**7-Hydroxy-8-hydroxyimino-7,8a-dimethyl-3,4,4a,7,-8,8a-hexahydro-1*H*-isoquinoline-2,5-dicarboxylic Acid 2-Benzyl Ester 5-Ethyl Ester (23).** Ketone **22** (190 mg, 0.47 mmol) was dissolved in pyridine (15 mL). After addition of hydroxylamine hydrochloride (1.644 g, 23.7 mmol), the reaction mixture was heated at 90−100 °C during 4 d. After cooling, a saturated aqueous solution of $NaHCO_3$ was added. After extraction with $CH_2Cl_2$ and evaporation of solvent, the crude product was purified by chromatography over silica gel (heptane/AcOEt 20/80) as eluent to give pure oxime **23** (140 mg, 0.33 mmol, 71% yield): IR (film) 3327, 2979, 2931, 1706, 1438, 1270, 1114, 1074 $cm^{-1}$; $^1H$ NMR (two rotamers, $CDCl_3$, 300 MHz) $\delta$ 1.04−1.22 (m, 1H), 1.08 (s, 3H), 1.32 (t, $J$ = 7.2 Hz, 3H), 1.71 (bs, 3H), 1.84 (bd, $J$ = 12.0 Hz, 1H), 2.53 (bd, $J$ = 13.4 Hz, 1H), 4.43 and 4.64 (bs, 1H), 2.61 (dd, $J$ = 3.7, 12.5 Hz, 1H), 2.72−2.92 (m, 1H), 4.11−4.33 (m, 3H, H-3), 4.87 (bd, $J$ = 13.4 Hz, 1H), 5.05−5.33 (m, 3H), 6.83 (bs, 1H), 7.27−7.50 (m, 5H); $^{13}C$ NMR (two rotamers, $CDCl_3$, 63 MHz) $\delta$ 14.3, 26.8, 27.6, 30.5, 40.7, 42.3, 44.1, 49.9, 61.1, 66.9 and 67.3, 69.6, 127.8 (2C), 127.9 (2C), 128.5 (2C), 130.1 and 130.4, 136.8 and 137.4, 142.3 and 142.8, 155.4, 161.0, 166.2; SM ($ES^+$) *m/z* (rel intensity) 855.3 (2M + $Na^+$, 16), 439.0 (M + $Na^+$, 100), 417.0 ($MH^+$, 20); HRMS (CI, isobutane) calcd for $C_{22}H_{29}N_2O_6$ ($MH^+$) 417.2025, found 417.2024.

**2-Benzyl-8a-(2-hydroxyethyl)-7-methyl-1,2,3,4,4a,8a-hexahydroisoquinoline-5-carboxylic Acid Ethyl Ester (28).** Under a nitrogen atmosphere, a solution of tetrahydropyridine **25** (379 mg, 1.05 mmol, see the Supporting Information for preparation) in $CH_2Cl_2$ (10 mL) was added to a solution of camphorsulfonic acid (348 mg, 1.50 mmol) in $CH_2Cl_2$ (10 mL). The reaction mixture was stirred during 5 min at room temperature and then concentrated. After a new addition of $CH_2Cl_2$ (12 mL), a solution of aminodiene **5** (218 mg, 1.030 mmol) in $CH_2Cl_2$ (10 mL) was added at 0 °C. After 15 h at 4 °C, the mixture was treated with a saturated $NaHCO_3$ aqueous solution (5 mL). The organic phase was collected and the aqueous phase extracted with $CH_2Cl_2$ (3 × 15 mL). The combined organic fractions were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude reaction mixture was dissolved in $CH_2Cl_2$ (20 mL), and then alumina (1.00 g) and acetaldehyde (1.19 mL, 21.0 mmol) were added. After the mixture was stirred for 20 h at room temperature, the resulting solution was filtered. This filtrate was treated during 1 h with an excess of $NaBH_4$ and MeOH (10 mL) at the same temperature. The reaction mixture was successively hydrolyzed under acidic conditions (pH <1) using $H_2O$ (50 mL) and HCl (1 N), basified with saturated aqueous $NaHCO_3$, and extracted with $CH_2Cl_2$ (3 × 15 mL). The organic fractions were dried over $MgSO_4$ and concentrated. Purification of the residue on silica gel (heptane/AcOEt: 4/1) gave the diene **28** as an oil (105 mg, 0.30 mmol, 28% yield): IR (film) 3424, 3061, 2934, 2802, 1702, 1266, 1025 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ 1.18−1.27 (m, 1H), 1.30 (t, $J$ = 6.9 Hz, 3 H), 1.40 (ddd, $J$ = 4.2, 12.5, 16.9 Hz, 1 H), 1.61−1.76 (m, 2 H), 1.82 (d, $J$ = 11.1 Hz, 1 H), 1.85−1.93 (m, 1 H), 1.86 (d, $J$ = 1.5 Hz, 3 H), 2.31 (ddd, $J$ = 1.1, 4.6, 11.8 Hz, 1 H), 2.72−2.80 (m, 1 H), 2.81 (d, $J$ = 11.1 Hz, 1 H), 3.41 (d, $J$ = 13.0 Hz, 1 H), 3.43−3.55 (m, 2 H), 3.64 (d, $J$ = 13.0 Hz, 1 H), 4.16−4.26 (m, 2 H), 5.61 (dd, $J$ = 1.2, 1.5 Hz, 1 H), 6.84 (d, $J$ = 1.2 Hz, 1 H), 7.20−7.37 (m, 5 H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ 14.4, 21.0, 27.5, 38.1, 38.8, 40.4, 52.5, 59.2, 60.5, 62.1, 63.5, 127.1, 128.3 (2C), 129.1 (2C), 130.2, 131.6, 135.2, 136.3, 138.2, 167.3; MS ($ES^+$) *m/z* (rel intensity) 356 ($MH^+$, 100); HRMS (CI, isobutane) calcd for $C_{22}H_{30}NO_3$ ($MH^+$) 356.2225, found 356.2207.

**8a-(2-Hydroxyethyl)-7-methyl-3,4,4a,8a-tetrahydro-1*H*-isoquinoline-2,5-dicarboxylic Acid 2-Benzyl Ester 5-Ethyl Ester (31).** The preparation of this compound was effected in three steps from diene **28**. **(1) Protection of the Primary Alcohol of Diene 28 as a TBDMS Derivative.** TBDMS-Cl (346 mg, 2.295 mmol) and imidazole (469 mg, 6.885 mmol) were added to a solution of diene **28** (163 mg, 0.459 mmol) in DMF (15 mL) at 0 °C. After being stirred for 45 h at room temperature, the reaction mixture was hydrolyzed with $H_2O$ (80 mL) and a saturated $NaHCO_3$ aqueous solution (60 mL) and finally extracted with $Et_2O$ (3 × 15 mL). The combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (heptane/AcOEt 95/5, 0.1% $NEt_3$) to give a colorless oil (209 mg, 0.446 mmol, 97% yield) of the protected alcohol: IR (film) 2929, 2856, 1705, 1252, 1230, 1094 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 300 MHz) $\delta$ −0.05 and −0.04 (s, 6 H), 0.83 (s, 9 H), 1.16−1.26 (m, 1 H), 1.32 (t, $J$ = 7.2 Hz, 3 H), 1.41 (ddd, $J$ = 4.2, 12.5, 16.9 Hz, 1 H), 1.61−1.74 (m, 2 H), 1.84 (d, $J$ = 11.6 Hz, 1 H), 1.84−1.93 (m, 1 H), 1.87 (d, $J$ = 1.3 Hz, 3 H), 2.30 (ddd, $J$ = 1.1, 4.1, 12.3 Hz, 1 H), 2.73−2.81 (m, 1 H), 2.88 (dd, $J$ = 1.6, 11.6 Hz, 1 H), 3.41 (d, $J$ = 13.3 Hz, 1 H), 3.41−3.55 (m, 2 H), 3.64 (d, $J$ = 13.3 Hz, 1 H), 4.14−4.29 (m, 2 H), 5.62 (d, $J$ = 1.2 Hz, 1 H), 6.84 (d, $J$ = 1.2 Hz, 1 H), 7.20−7.37 (m, 5 H); $^{13}C$ NMR ($CDCl_3$, 75 MHz) $\delta$ −5.3 (2C), 14.4, 18.3, 21.0, 26.1 (3C), 27.6, 38.3, 39.1, 40.2, 52.6, 59.6, 60.4, 62.2, 63.6, 127.0, 128.3 (2C), 129.1 (2C), 129.7, 131.5, 135.3, 137.0, 138.5, 167.3; MS ($ES^+$) *m/z* (rel intensity) 470 ($MH^+$, 100); HRMS (CI, isobutane) calcd for $C_{28}H_{44}NO_3Si$ ($MH^+$) 470.3091, found 470.3094. **(2) Exchange of the Benzyl Group with a Cbz Protecting Group.** Under a nitrogen atmosphere, benzyl chloroformate (0.66 mL, 3.940 mmol) was added dropwise to a solution of the above silylated diene (185 mg, 0.394 mmol) in $CH_2Cl_2$ (20 mL) at 0 °C. The reaction mixture was then stirred during 4 d at room temperature. Concentration in vacuo, followed by purification of the residue by chromatography on silica gel (heptane/AcOEt: gradient from 95/5 to 90/10, 0.1% $NEt_3$), gave a colorless oil (194 mg, 0.378 mmol, 96% yield): IR (film) 2953, 2929, 2857, 1703, 1234, 1077 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 300 MHz) $\delta$ 0.01 (s, 6 H), 0.86 (s, 9 H), 1.16−1.28 (m, 1 H), 1.26 (t, $J$ = 7.0 Hz, 3 H), 1.54−1.77 (m, 3 H), 1.77 (bs, 3 H), 2.50 (dd, $J$ = 4.4, 11.8 Hz, 1 H), 2.56−2.86 (m, 2 H), 3.47−3.69 (m, 2 H), 3.94−4.05 (m, 1 H), 4.09−4.28 (m, 2 H), 4.35 (bd, $J$ = 13.2 Hz, 1 H), 5.01−5.24 (m, 2 H), 5.66 (bs, 1 H), 6.80 (s, 1 H), 7.27−7.42 (m, 5 H); $^{13}C$ NMR ($CD_3CN$, 63 MHz) $\delta$ −5.3 (2C), 14.5, 18.7, 20.9, 26.3 (3C), 27.6, 39.2, 39.7, 40.5, 44.0, 52.5, 60.2, 61.2, 67.3, 128.7, 128.8 (2C), 129.4 (2C), 132.5, 132.8, 134.8, 135.3, 138.5, 156.0, 167.4; MS ($ES^+$) *m/z* (rel intensity) 552 ($MK^+$, 24), 536 ($MNa^+$, 100), 514 ($MH^+$, 23); MS (CI, isobutane) *m/z* (rel intensity) 604 (82), 514 ($MH^+$, 100), 456 (96), 91 (60); HRMS (CI, isobutane) calcd for $C_{29}H_{44}NO_5Si$ ($MH^+$) 514.2989, found 514.2982. **(3) Final Hydrolysis of the Protecting TBDMS Group To Give Alcohol 31.** A TBAF solution (1 M in THF, 5% $H_2O$, 0.70 mL, 0.697 mmol) was added dropwise to a cold solution of the above silylated carbamate (179 mg, 0.348 mmol) in THF (10 mL). After 15 min, the mixture was allowed to warm to room temperature over 2 h. After addition of $H_2O$ (20 mL) and basification with a saturated $NaHCO_3$ aqueous solution, the mixture was extracted with $CH_2Cl_2$ (3 × 15 mL). The combined $CH_2Cl_2$ extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on silica gel (heptane/AcOEt 3/2, 0.1% $NEt_3$) gave carbamate **31** (129 mg, 0.323 mmol, 93% yield): IR (film) 3467, 2941, 2920, 1698, 1442, 1263,

1230 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 300 MHz) $\delta$ 1.17−1.28 (m, 1 H), 1.26 (t, $J$ = 7.2 Hz, 3 H), 1.55−1.78 (m, 3 H), 1.77 (bs, 3 H), 2.51 (dd, $J$ = 4.6, 11.8 Hz, 1 H), 2.57−2.86 (m, 2 H), 3.36−3.57 (m, 2 H), 3.95−4.02 (m, 1 H), 4.17 (q, $J$ = 7.2 Hz, 2 H), 4.26 (bd, $J$ = 13.3 Hz, 1 H), 5.01−5.24 (m, 2 H), 5.63 (bs, 1 H), 6.80 (s, 1 H), 7.27−7.44 (m, 5 H); $^{13}C$ NMR ($CD_3CN$, 63 MHz) $\delta$ 14.6, 20.9, 27.6, 39.0, 40.0, 40.4, 44.1, 52.4, 58.7, 61.3, 67.3, 128.5, 128.8 (2C), 129.4 (2C), 132.5, 132.9, 134.8, 135.3, 138.5, 156.0, 167.5; MS ($ES^+$) $m/z$ (rel intensity) 438 ($MK^+$, 58), 422 ($MNa^+$, 100); HRMS (CI, isobutane) calcd. for $C_{23}H_{30}NO_5$ ($MH^+$) 400.2124, found 400.2103.

**8a-(2-Methanesulfonyloxyethyl)-7-methyl-3,4,4a,8a-tetrahydro-1*H*-isoquinoline-2,5-dicarboxylic Acid 2-Benzyl Ester 5-Ethyl Ester (32).** Methylsulfonyl chloride (0.14 mL, 1.765 mmol) and triethylamine (0.49 mL, 3.53 mmol) were added to a solution of alcohol **31** (141 mg, 0.353 mmol) in $CH_2Cl_2$ (25 mL) at −78 °C. After 5 min, the reaction mixture was allowed to warm to 0 °C over 30 min and then stirred during 1 h at the same temperature. $H_2O$ (20 mL) was added, the mixture was basified with a saturated $NaHCO_3$ aqueous solution (10 mL), and the organic phase was collected. After extraction of the aqueous phase with $CH_2Cl_2$ (4 × 10 mL), the combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo. Chromatography on silica gel (heptane/AcOEt 7/3) of the residue gave mesylate **32** (163 mg, 0.341 mmol, 96% yield): IR (film) 2979, 2939, 1698, 1356, 1274, 1235, 1174 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 300 MHz) $\delta$ 1.08−1.28 (m, 1 H), 1.26 (t, $J$ = 7.0 Hz, 3 H), 1.42−1.52 (m, 1 H), 1.58−1.68 (m, 1 H), 1.79 (bs, 3 H), 1.83−1.92 (m, 1 H), 2.53 (dd, $J$ = 3.5, 12.3 Hz, 1 H), 2.59−2.87 (m, 2 H), 2.94 (bs, 3 H), 3.94−4.04 (m, 1 H), 4.04−4.29 (m, 5 H), 5.00−5.26 (m, 2 H), 5.61 (bs, 1 H), 6.82 (s, 1 H), 7.27−7.48 (m, 5 H); $^{13}C$ NMR ($CD_3CN$, 75 MHz) $\delta$ 14.5, 20.9, 27.6, 36.0, 37.3, 38.8, 40.1, 43.9, 52.0, 61.4, 67.4, 68.0, 128.7, 128.8 (2C), 129.4 (2C), 132.6, 134.1, 133.1, 135.2, 138.4, 156.0, 167.2; MS (CI, isobutane) $m/z$ (rel intensity) 478 ($MH^+$, 92), 434 (50), 338 (62), 91 (100); HRMS (CI, isobutane) calcd for $C_{24}H_{32}NO_7S$ ($MH^+$) 478.1899, found 478.1877.

**4-Methyl-1,3a,6,6a,7,8-hexahydro-3,9-diazacyclopenta-[*d*]naphthalene-6,9-dicarboxylic Acid 9-Benzyl Ester 6-Ethyl Ester (33 and 34).** Under a nitrogen atmosphere, $NaN_3$ (150 mg, 2.3 mmol) was added to a solution of mesylate **32** (110 mg, 0.231 mmol) in DMF (20 mL). The reaction mixture was stirred during 24 h at 60 °C and then allowed to cool to room temperature. $H_2O$ (200 mL) was added before extraction with $Et_2O$ (5 × 20 mL). The combined etheral extracts were dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography on silica gel (heptane/AcOEt 1/1, 0.1% $NEt_3$) of the residue allowed separation of the two isomers. Major isomer **33** (38 mg, 0.096 mmol, 42% yield): IR (film) 2979, 2940, 2858, 1729, 1698, 1436, 1264 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 400 MHz) $\delta$ 1.25−1.42 (m, 2 H), 1.27 (t, $J$ = 7.1 Hz, 3 H), 1.81 (s, 3 H), 2.18 (d, $J$ = 17.0 Hz, 1 H), 2.33−2.39 (m, 1 H), 2.61 (d, $J$ = 13.3 Hz, 1 H), 2.70 (d, $J$ = 17.0 Hz, 1 H), 2.77−2.84 (m, 1 H), 3.38−3.41 (m, 1 H), 3.88 (dd, $J$ = 2.0, 13.3 Hz, 1 H), 4.10−4.26 (m, 4 H), 5.13 (bs, 2 H), 5.52 (s, 1 H), 7.32−7.41 (m, 5 H), 7.53 (s, 1 H); $^{13}C$ NMR ($CD_3CN$, 101 MHz) $\delta$ 14.8, 21.6, 25.5, 39.1, 43.5, 44.6 (2C), 45.5, 53.1, 61.6, 67.8, 75.1, 118.5, 128.8, 129.0 (2C), 129.7 (2C), 137.4, 138.7, 156.5, 167.0, 174.2; MS ($ES^+$) $m/z$ (rel intensity) 435 ($MK^+$, 28), 419 ($MNa^+$, 100), 397 ($MH^+$, 15); HRMS (CI, isobutane) calcd for $C_{23}H_{29}N_2O_4$ ($MH^+$) 397.2127, found 397.2140. Minor isomer **34** (23 mg, 0.058 mmol, 25% yield): IR (film) 2936, 2856, 1722, 1698, 1435, 1221 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 400 MHz) $\delta$ 1.26 (t, $J$ = 7.1 Hz, 3 H), 1.45−1.52 (m, 1 H), 1.75−1.85 (m, 1 H), 1.89−1.95 (m, 1 H), 1.96 (s, 3 H), 2.48 (d, $J$ = 18.0 Hz, 1H), 2.68 (dd, $J$ = 1.4, 18.0 Hz, 1 H), 3.15 (d, $J$ = 13.3 Hz, 1 H), 3.23−3.31 (m, 2 H), 3.56 (d, $J$ = 13.3 Hz, 1 H), 3.72−3.80 (m, 2 H), 4.16 (q, $J$ = 7.1 Hz, 2 H), 5.14 (s, 2 H), 5.49 (s, 1 H), 7.32−7.42 (m, 5 H), 7.46 (s, 1 H); $^{13}C$ NMR ($CD_3CN$, 101 MHz) $\delta$ 14.7, 22.2, 26.7, 35.8, 41.5, 44.2 (2C), 48.8, 50.0, 61.9, 67.8, 77.5, 120.5, 128.9, 129.1 (2C), 129.7 (2C), 136.5, 138.9, 156.4, 166.1, 175.0; MS ($ES^+$) $m/z$ (rel intensity) 435 ($MK^+$, 31), 419 ($MNa^+$, 100), 397 ($MH^+$, 98); HRMS (CI, isobutane) calcd for $C_{23}H_{29}N_2O_4$ ($MH^+$) 397.2127, found 397.2123.

**4-Methyl-1,2,3,3a,6,6a,7,8-octahydro-3,9-diazacyclopenta[*d*]naphthalene-6,9-dicarboxylic Acid 9-Benzyl Ester 6-Ethyl Ester (38a).** $NaBH_4$ (16 mg, 0.430 mmol) was added to a cold solution of imine **33** (17 mg, 0.043 mmol) in $CH_2Cl_2$/MeOH (1:1, 2 mL). The reaction mixture was allowed to warm to room temperature during 30 min and then poured into an aqueous HCl solution (25 mL, pH 1−2). Hydrolysis was achieved by supplementary dropwise HCl (1 N) addition to pH 1. The mixture was basified with a saturated $NaHCO_3$ solution and extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by preparative TLC (AcOEt/MeOH 100:1, 0.2% $NEt_3$) gave amine **38a** (14 mg, 0.035 mmol, 82% yield): IR (film) 3340, 2940, 2876, 1731, 1698, 1436, 1196 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 400 MHz, 60 °C) $\delta$ 1.24 (t, $J$ = 7.1 Hz, 3 H), 1.24−1.34 (m, 3 H), 1.66 (bs, 3 H), 1.72−1.79 (m, 1 H), 2.20−2.25 (m, 1 H), 2.52 (d, $J$ = 13.4 Hz, 1 H), 2.57−2.64 (m, 1 H), 2.73−2.81 (m, 1 H), 2.88−2.94 (m, 1 H), 3.10 (bs, 1 H), 3.42−3.46 (m, 1 H), 4.08−4.20 (m, 4 H), 5.08 (bd, $J$ = 12.6 Hz, 1 H), 5.14 (bd, $J$ = 12.6 Hz, 1 H), 5.56 (d, $J$ = 1.3 Hz, 1 H), 7.30−7.40 (m, 5 H); $^{13}C$ NMR ($CD_3CN$, 63 MHz) $\delta$ 14.5, 20.8, 25.4, 34.5, 40.5, 42.9, 44.0, 44.3, 47.0, 53.2, 60.1, 61.2, 67.3, 119.8, 128.5, 128.8 (2C), 129.4 (2C), 136.7, 138.5, 155.8, 174.4; MS ($ES^+$) $m/z$ (rel intensity) 819 ($[2M + Na]^+$, 31), 797 ($[2M + H]^+$, 100), 421 ($MNa^+$, 10), 399 ($MH^+$, 47).

**4-Methyl-1,2,3,3a,6,6a,7,8-octahydro-3,9-diazacyclopenta[*d*]naphthalene-6,9-dicarboxylic Acid 9-Benzyl Ester 6-Ethyl Ester (38b).** $NaBH_4$ (32 mg, 0.860 mmol) was added to a cold solution of imine **34** (34 mg, 0.086 mmol) in $CH_2Cl_2$/MeOH (1:1, 4 mL). The reaction mixture was allowed to warm to room temperature during 30 min and then poured into an aqueous HCl solution (50 mL, pH 1−2). The mixture was basified with a saturated $NaHCO_3$ aqueous solution and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo. Purification of the residue by preparative TLC ($CH_2Cl_2$/MeOH 95/5, 0.2% $NEt_3$) gave amine **38b** (30 mg, 0.075 mmol, 88% yield): IR (film) 3333, 2937, 2870, 1731, 1694, 1435, 1220 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 400 MHz) $\delta$ 1.22 (t, $J$ = 7.1 Hz, 3 H), 1.40−1.47 (m, 1 H), 1.49−1.58 (m, 1 H), 1.59−1.85 (m, 2 H), 1.74 (bs, 3 H), 1.95−2.01 (m, 1 H), 2.15 (bs, 1 H), 2.65−2.80 (m, 2 H), 2.84−3.09 (m, 2 H), 3.15−3.29 (m, 2 H), 3.33 (bd, $J$ = 11.0 Hz, 1 H), 3.64−3.76 (m, 1 H), 4.12 (q, $J$ = 7.1 Hz, 2 H), 5.09 (s, 2 H), 5.44 (bs, 1 H), 7.27−7.40 (m, 5 H); $^{13}C$ NMR ($CD_3CN$, 63 MHz) $\delta$ 14.5, 21.8, 26.5, 37.4, 37.7, 41.0, 44.4, 44.9, 45.5, 49.3, 61.5, 64.5, 67.4, 120.3, 128.5, 128.8 (2C), 129.4 (2C), 136.6, 138.4, 156.1, 175.0; MS ($ES^+$) $m/z$ (rel intensity) 797 ($[2M + H]^+$, 14), 399 ($MH^+$, 100); HRMS (CI, isobutane) calcd for $C_{23}H_{31}N_2O_4$ ($MH^+$) 399.2284, found 399.2288.

**4-Hydroxy-4-methyl-1,2,3,3a,4,6a,7,8-octahydro-3,9-diazacyclopenta[*d*]naphthalene-6,9-dicarboxylic Acid 9-Benzyl Ester 6-Ethyl Ester (40).** Trifluoroacetic anhydride (0.210 mL, 1.506 mmol) was added slowly, at 0 °C, to a solution of hydrogen peroxide (50% in $H_2O$, 0.044 mL, 0.753 mmol) in $CH_2Cl_2$ (5 mL). The resulting mixture was stirred during 90 min at 0 °C. To an aliquot of this freshly prepared peroxide solution (0.75 mL) was added, at 0 °C, a solution of amine **38a** (18 mg, 0.045 mmol) dissolved in a mixture of trifluoroacetic acid and $CH_2Cl_2$ (1:50, 0.45 mL, corresponding to 0.113 mmol of the acid). The reaction mixture was allowed to warm to room temperature during 45 min, poured into a cold saturated $Na_2SO_3$ solution, and basified with a saturated $NaHCO_3$ solution. The two phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic fractions were dried over $MgSO_4$ and concentrated in vacuo. This freshly prepared crude epoxide was then taken up in anhydrous EtOH (0.50 mL). A solution of NaOEt in EtOH (1.50 mL), prepared from Na (42 mg, 1.826 mmol) and anhydrous EtOH (10 mL), was added at 0 °C. After stirring for 6 h at room temperature the reaction mixture was poured into cold $H_2O$ (20 mL) and extracted with $CH_2Cl_2$ (4 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by preparative TLC ($CH_2Cl_2$/MeOH 95/5, 0.2% $NEt_3$) to give amino alcohol **40** (15 mg, 0.036 mmol, 80% yield): IR (film)

3378, 2959, 2935, 2887, 1702, 1438, 1257 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 400 MHz, 60 °C): $\delta$ 1.11 (s, 3 H), 1.16 (ddd, $J$ = 4.7, 12.8, 17.6 Hz, 1 H), 1.27 (t, $J$ = 7.1 Hz, 3 H), 1.38 (dd, $J$ = 7.3, 12.8 Hz, 1 H), 1.55−1.64 (m, 1 H), 1.82−1.88 (m, 1 H), 2.69 (d, $J$ = 13.6 Hz, 1 H), 2.74−2.81 (m, 2 H), 2.89 (ddd, $J$ = 2.5, 13.0, 13.0 Hz, 1 H), 2.99−3.07 (m, 2 H), 4.07 (d, $J$ = 13.6 Hz, 1 H), 4.10−4.23 (m, 3 H), 5.08−5.21 (m, 2 H), 6.71 (s, 1 H), 7.32−7.41 (m, 5 H); $^{13}C$ NMR ($CD_3CN$, 63 MHz) $\delta$ 14.4, 31.8, 32.4, 34.4, 37.9, 44.1, 44.9, 47.1, 52.1, 61.4, 64.5, 65.9, 67.4, 128.9 (2C), 129.5 (2C), 130.3, 138.5, 144.8, 167.5; MS ($ES^+$) *m*/*z* (rel intensity) 415 ($MH^+$, 100); HRMS (CI, isobutane) calcd for $C_{23}H_{31}N_2O_5$ ($MH^+$) 415.2233, found 415.2230. Compound **40** (7 mg, 0.017 mmol, 84% yield) was also prepared from amine **38b** (8 mg, 0.020 mmol) according to the procedure used for amine **38a**.

**Oxazolidine Derivative 41.** To a solution of amino alcohol **40** (8.0 mg, 0.019 mmol) in $CH_3CN$ (1 mL) was added, under a nitrogen atmosphere, an aqueous formaldehyde solution (37%, 0.1 mL) and then dropwise a mixture of AcOH/$CH_3CN$ (1/9) in order to adjust pH to 2−4. The reaction mixture was then stirred during 15 h at room temperature. After addition of a saturated $NaHCO_3$ solution (10 mL), the aqueous phase was extracted with $CH_2Cl_2$ (4 × 5 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The residue was filtered on alumina ($Et_2O$) to give oxazolidine derivative **41** (7.5 mg, 0.018 mmol, 91% yield): IR (film) 2982, 2934, 2418, 1713, 1698, 1435, 1258, 1145 $cm^{-1}$; $^1H$ NMR ($CD_3CN$, 400 MHz) $\delta$ 1.06 (ddd, $J$ = 4.8, 12.9, 17.8 Hz, 1 H), 1.29 (t, $J$ = 7.1 Hz, 3 H), 1.49 (s, 3 H), 1.69−1.76 (m, 1 H), 1.82−1.90 (m, 1 H), 1.95−2.03 (m, 1 H), 2.78 (dd, $J$ = 4.7, 12.7 Hz, 1 H), 2.77−2.88 (m, 2 H), 3.21−3.33 (m, 2 H), 3.60 (bs, 1 H), 4.09−4.17 (m, 1 H), 4.21 (q, $J$ = 7.1 Hz, 2 H), 4.34 (d, $J$ = 6.1 Hz, 1 H), 4.51 (d, $J$ = 13.7 Hz, 1 H), 4.74 (d, $J$ = 6.1 Hz, 1 H), 5.11 (d, $J$ = 12.6 Hz, 1 H), 5.21 (d, $J$ = 12.6 Hz, 1 H), 6.78 (s, 1 H), 7.31−7.45 (m, 5 H); $^{13}C$ NMR ($CD_3CN$, 75 MHz) $\delta$ 14.4, 26.1, 31.7, 35.3, 38.4, 44.2, 46.4, 52.4, 57.9, 62.0, 67.7, 78.0, 82.3, 89.4, 128.7, 128.8 (2C), 129.4 (2C), 136.1, 138.2, 139.3, 156.1, 166.1; MS (CI) *m*/*z* (rel intensity) 427 ($MH^+$, 100), 383 (41), 291 (32), 91 (45); HRMS (CI, isobutane) calcd. for $C_{24}H_{31}N_2O_5$ ($MH^+$) 427.2233, found 427.2246.

**Supporting Information Available:** Experimental procedure for preparation of tetrahydropyridine **25**. Copies of $^1H$ and $^{13}C$ NMR spectra of derivatives **10**, **13**, **18**, **19a**,**b**, **20**, and **23** and with attribution of signals of derivatives **25**, **28**, **31**−**34**, **38a**,**b**, **40**, and **41**. Schemes showing observed NOEs for key compounds **20**, **33,** and **41**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0162033