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Synthesis of the ABC Ring System of Manzamine A

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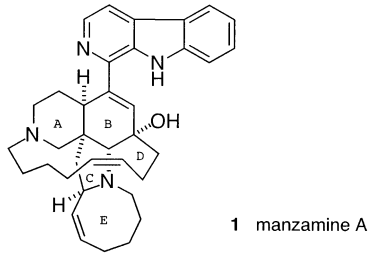
Received December 14, 2001

A synthesis of the core ABC ring system of the manzamine alkaloids is described, starting from arecoline. The key steps involve a Claisen rearrangement to set up a 4-substituted-3-methylene-piperidine and a stereoselective azomethine ylide dipolar cycloaddition reaction. Condensation of the aldehyde **6** and sarcosine ethyl ester hydrochloride salt gives an intermediate azomethine ylide, which undergoes an intramolecular cycloaddition reaction to set up two new rings and three new chiral centers stereoselectively. The aldehyde **6** was not a suitable substrate for related azomethine ylide cycloaddition reactions with other amines. However, the related dimethyl acetal **26** could be condensed with a variety of amines to give the desired tricyclic products. The cycloaddition reaction with *N*-methyl or *N*-allyl glycine ethyl ester gave almost exclusively the exo adduct, whereas cycloaddition with glycine ethyl ester gave the endo adduct.

Introduction

The alkaloid manzamine A **1** (Figure 1), first isolated in 1986 from the marine sponge of the genus *Haliclona*,[1] consists of a complex pentacyclic ring system, with a pendant β-carboline moiety. Many related alkaloids of the manzamine family have since been isolated.[2,3] The unusual structure of manzamine A and its potent biological activity, particularly as an antitumor agent and more recently as an antimalarial,[4] has prompted significant synthetic studies in this area.[5,6] Two successful total syntheses have been reported to date, and make use of intramolecular [2+2] or [4+2] cycloaddition chemistry as key steps to set up ring B.[7] Recently, we reported an efficient intramolecular [3+2] cycloaddition reaction to set up ring C of the manzamine alkaloids.[8] This paper reports full details of this work and its extension to other substituted tricyclic compounds that make up the ABC ring system of manzamine A.



1 manzamine A

FIGURE 1. Structure of manzamine A.

Manzamine A contains a pyrrolidine ring C fused to the six-membered ring B, the eight-membered ring E, and spiro-fused to the piperidine ring A. Retrosynthetic analysis of manzamine A leads to the tetracyclic ABCE ring system **2** (Scheme 1). Further disconnection, to an azomethine ylide such as **3**, makes use of the [3+2] cycloaddition reaction as the key step in a novel route to the required core of manzamine A. This chemistry sets up ring B simultaneous with the pyrrolidine ring C and represents a highly efficient entry to this ring system.

Intramolecular cycloaddition reactions of azomethine ylides allow rapid access to bicyclic and polycyclic nitrogen-

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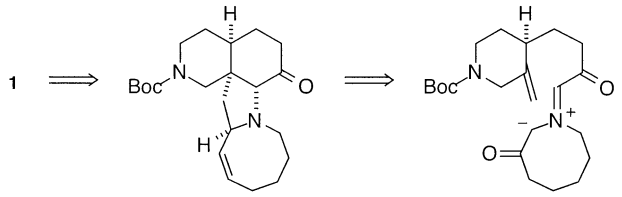
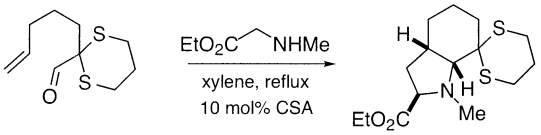
10.1021/jo016376s CCC: $22.00
Published on Web 07/27/2002

SCHEME 1



SCHEME 2



containing rings.[9] We anticipated that cycloaddition of the azomethine ylide (such as **3**) would take place stereoselectively to give the desired stereoisomer of the product. Approach of the tethered azomethine ylide to the *exo*-methylene unit on the same face of the piperidine ring A leads to the cis-fused AB ring system. Cycloaddition would then set up the thermodynamically more stable cis-fused BC ring system. A convenient method for the preparation of azomethine ylides uses the condensation of a secondary amine and an aldehyde and model studies have showed that the BC ring system **5** could be prepared from the aldehyde **4** (Scheme 2).[10] The expected product **5** with the correct relative stereochemistry was obtained as the major product in this intramolecular cycloaddition reaction. Other reports of related cycloaddition reactions support the feasibility and stereoselectivity of the proposed route to manzamine A.[11]

Results and Discussion

The precedent provided by the successful intramolecular cycloaddition reaction of the unsaturated aldehyde **4** with *N*-methyl glycine (sarcosine) ethyl ester led us to propose a route to the manzamine alkaloids using the unsaturated aldehyde **6** and a secondary amine (Figure 2). A number of synthetic routes to compound **6** were explored and our favored strategy, outlined below, makes use of a sigmatropic rearrangement to set up the required *exo*-methylene-substituted piperidine ring.

The route to the cycloaddition precursor **6** starts from arecoline **7**, obtained by base-extraction of commercially available arecoline hydrobromide. The *N*-methyl group can be removed by using a procedure reported by Olofson and co-workers.[12] Treatment of arecoline with α-chloroethyl chloroformate in refluxing toluene gave the α-chloroethyl carbamate, which was heated in methanol to give the free amine **8** (Scheme 3). The α-chloroethyl carbamate was isolated only by extraction and was not purified; likewise the amine **8** was taken on directly in the next step without purification. Protection of the amine **8** with di-*tert*-butyl dicarbonate gave the *N*-Boc protected compound **9**. Purification at this stage, by column chromatography, resulted in a good isolated yield of the product **9**. The ester **9** could be reduced with $LiAlH_4$ to give the alcohol **10**, although a cleaner and more reproducible reduction was obtained by using the reducing agent diisobutylaluminum hydride (DIBAL-H). Subjecting the alcohol **10** to the Johnson−Claisen rearrangement[13,14] with triethyl orthoacetate gave the *exo*-methylene-substituted piperidine ester **11**. Alternatively, the Claisen rearrangement with ethyl vinyl ether and mercury acetate gave the aldehyde **12**. The chemistry provides a rapid access to the desired *exo*-methylene-substituted piperidine unit, required for the later cycloaddition reaction.

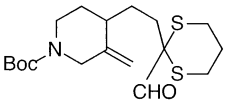
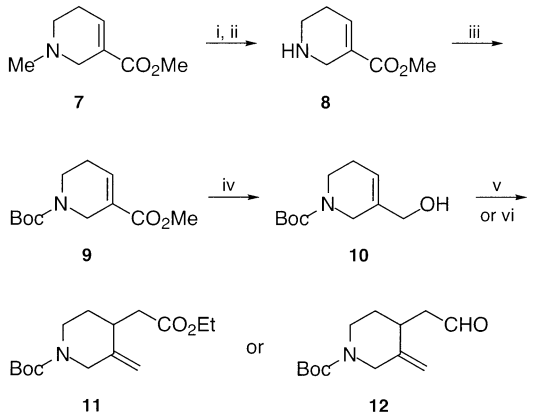


FIGURE 2. Aldehyde substrate for the cycloaddition reaction.

SCHEME 3[a]



[a] Key: (i) MeCH(Cl)OCOCl, PhMe, heat; (ii) MeOH, heat; (iii) Boc_2O, CH_2Cl_2, Et_3N, 78% over 3 steps; (iv) DIBAL-H, THF, −78 °C, 85%; (v) $MeC(OEt)_3$, xylene, 2,4-dinitrophenol, heat, **11** 63%, or (vi) CH_2=CHOEt, $Hg(OAc)_2$, xylene, 135 °C, **12** 79%.

The ester **11** could alternatively be accessed by altering the order of steps and conducting the reduction of arecoline and Claisen rearrangement prior to demethylation and carbamate protection. However, yields were more consistent, due to easier purification, using the route described in Scheme 3.

The ester **11** and the aldehyde **12** were reduced with $LiAlH_4$ to the alcohol **13** (Scheme 4). Conversion to the

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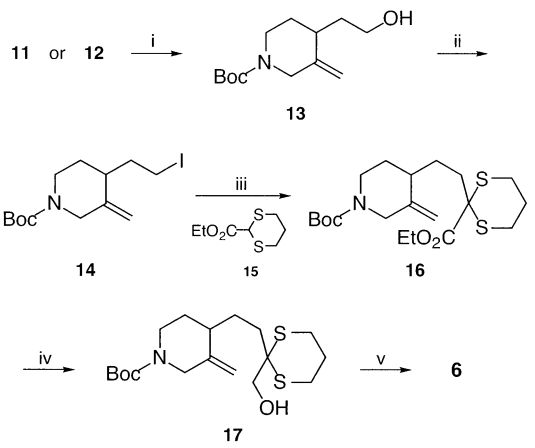
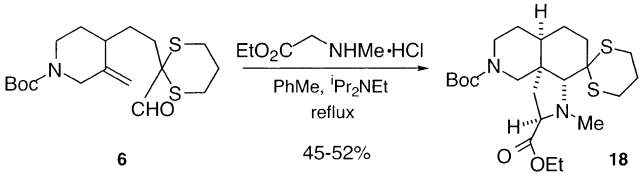
SCHEME 4[a]



[a] Key: (i) LiAlH, THF, from **11** 89%, from **12** 98%; (ii) I_2, Ph_3P, imidazole, THF, 81% or CBr_4, Ph_3P, CH_2Cl_2, then NaI, acetone, 80-95%; (iii) *n*-BuLi, THF, HMPA, dithiane **15** followed by addition of the iodide **14**, −40 °C to rt, 96%; (iv) LiAlH, THF, 94%; (v) 2.2 equiv of $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C then Et_3N, 85%.

SCHEME 5



iodide **14** was achieved directly with triphenylphosphine and iodine or via the corresponding bromide with triphenylphosphine and CBr_4 then NaI in acetone. The remaining two carbon atoms were added in the form of the dithiane **15**. This step was best achieved by using the iodide **14** rather than the corresponding bromide. Deprotonation of the dithiane with *n*-BuLi in the presence of the additive HMPA gave the adduct **16**; best yields were obtained in the presence of more than 4 equiv of this additive, although lower yields could be obtained with less than 4 equiv or even in its absence (**16**, 30%).[15] Reduction of the ester **16** to the alcohol **17** and Swern oxidation gave the desired aldehyde **6**.

Initial attempts to promote the cycloaddition reaction of the aldehyde **6** were unsuccessful. Under the conditions used for the cycloaddition of the aldehyde **4** with a secondary amine such as *N*-methyl glycine ethyl ester, no identifiable products were isolated. Changing from toluene to other nonpolar or polar solvents or the addition of a Lewis acid did not provide any of the desired cycloadduct. However, on changing to the use of the hydrochloride salt of *N*-methyl glycine ethyl ester, with heating in toluene and diisopropylethylamine, a reasonable yield (45−52%) of the cycloadduct **18** was obtained (Scheme 5). A small amount of another product was isolated, which showed (by ^1H NMR spectroscopy) the presence of the *exo*-methylene group, although its identity could not be determined. The remaining material was at least in part polymeric and too polar to be isolated.

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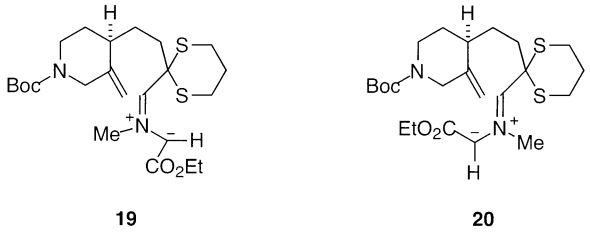


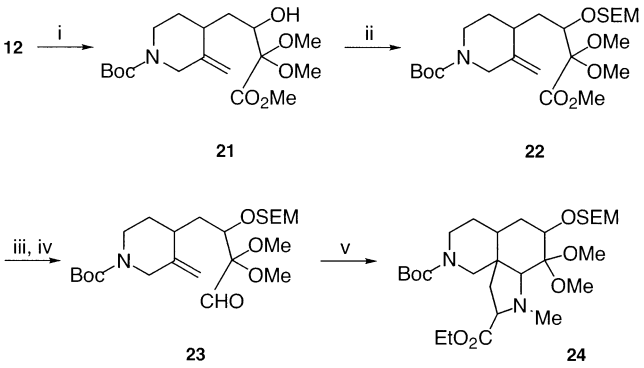
FIGURE 3. Azomethine ylide(s) required for the formation of **18**.

The cycloadduct **18** was obtained as a single diastereomer and its stereochemistry was determined by a single-crystal X-ray diffraction study.[8] The X-ray confirmed the relative stereochemistry as depicted and as required for the natural product manzamine A. Hence, the condensation of the aldehyde **6** and *N*-methyl glycine ethyl ester must have occurred under these conditions to give the necessary azomethine ylide. Cycloaddition then takes place with the anticipated formation of the cis-fused AB and BC rings. In addition, the isomer with the ethyl ester group in the exo rather than the endo position has been generated, in line with that formed from aldehyde **4** (Scheme 2). This implies that the cycloaddition reaction takes place through an *S*-shaped ylide **19** or **20** (Figure 3).

The intramolecular azomethine ylide cycloaddition reaction with the aldehyde **6** provides a rapid entry to the desired tricyclic ABC ring system of manzamine A. We had been successful in performing the cycloaddition reaction using the model aldehyde **4** with a range of amines.[10] However, we found that condensation of the aldehyde **6** with these amines gave rise predominantly to the recovered aldehyde **6** together with decomposition products and only trace amounts at best of the desired cycloaddition products. Cycloaddition was unsuccessful with different substituted or unsubstituted glycine derivatives (as the free base or hydrochloride salt), other than that with *N*-methyl glycine ethyl ester hydrochloride and diisopropylethylamine. Attempts to remove the *N*-methyl group with α-chloroethyl chloroformate from the product **18** (or from the alcohol or its *tert*-butyl dimethylsilyl ether formed by reduction of the ester **18**) were unsuccessful. We therefore needed to alter the substrate aldehyde **6** if we were going to make further progress toward the synthesis of the natural product.

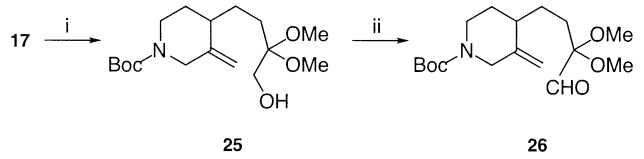
We postulated that the dithiane functional group was detrimental to the cycloaddition reaction and we therefore investigated alternative functionality α to the required aldehyde group. Alkylation of the enolate generated from methyl dimethoxyacetate and lithium diisopropylamide with the iodide **14** was unsuccessful; however, this enolate did add to the aldehyde **12** to give a diastereomeric mixture (1:1) of the esters **21** (Scheme 6). Reduction of the ester **21** gave a complex mixture of products and we therefore investigated protecting the alcohol group. The hindered nature of this functional group presumably prevented the incorporation of a selection of protecting groups, but finally it was found that the trimethylsilylethoxymethyl (SEM) derivative **22** could be prepared. Subsequent ester reduction and Swern oxidation gave the aldehyde **23**. Cycloaddition of the aldehyde **23** with *N*-methyl glycine ethyl ester hydro-

SCHEME 6[a]



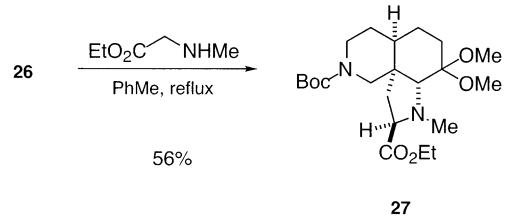
[a] Key: (i) $MeO_2CCH(OMe)_2$, LDA, THF, −78 °C, 86%; (ii) SEMCl, $^iPr_2NEt$, CH_2Cl_2, 81%; (iii) $LiAlH_4$, Et_2O; (iv) 2.2 equiv of $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C then Et_3N, 71% over two steps; (v) $EtO_2CCH_2NHMe\cdot HCl$, PhMe, $^iPr_2NEt$, reflux, 65−70%.

SCHEME 7[a]



[a] Key: (i) NCS, $AgNO_3$, collidine, THF, MeOH, 0 °C; (ii) 2.2 equiv of $(COCl)_2$, DMSO, CH_2Cl_2, −60 °C then Et_3N, 51−60% over two steps.

SCHEME 8

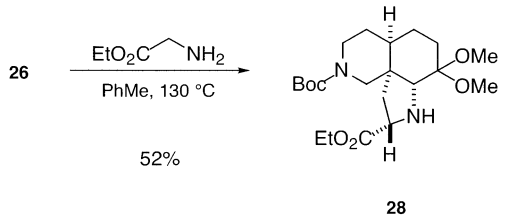


chloride was successful in giving the adduct **24** in improved yield (65−70%). However, this product was a mixture of at least three inseparable diastereomers and in addition, it was not possible to cleave the SEM group under a variety of conditions. We therefore sought an alternative route, avoiding problems with mixtures of diastereomeric substrates.

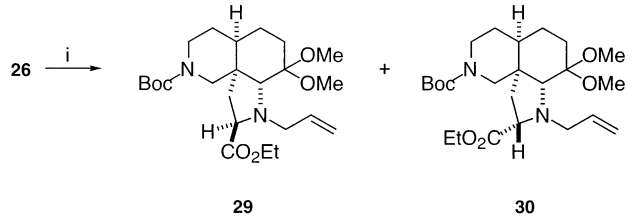
We were interested in preparing a substrate with a dimethyl acetal group α to the aldehyde and found that treatment of the dithiane **17** with *N*-chlorosuccinimide and $AgNO_3$ in methanol gave the desired acetal **25** (Scheme 7). This compound was not purified, but was oxidized directly to the required aldehyde **26**. We were now in a position to investigate the cycloaddition reaction with this new aldehyde and were pleased to find that it tolerated a much wider selection of amines.

Condensation of the aldehyde **26** with *N*-methyl glycine ethyl ester in toluene and a Dean−Stark apparatus resulted in the formation of the desired cycloadduct **27** (Scheme 8). A small amount of another diastereomer was also formed but was not purified. The major product, isomer **27**, had the desired stereochemistry, as it was identical (by NMR spectroscopy) with the product obtained on conversion (80%) of the dithiane **18** to the same

SCHEME 9

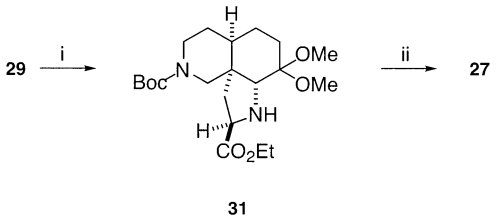


SCHEME 10[a]



[a] Key: (i) $EtO_2CCH_2NHCH_2CH{=}CH_2$, PhMe, reflux **29** 43%, **30** 6%.

SCHEME 11[a]



[a] Key: (i) $Pd(dba)_2$, dppb, thiosalicyclic acid, THF, rt, 86%; (ii) MeI, DMF, K_2CO_3, 71%.

acetal **27** with $HgO/HgCl_2$. As an X-ray of the dithiane **18** had been obtained, we were confident that the stereochemistry of the product **27** was as depicted, with the desired cis-fused AB and BC rings and with the ethyl ester group located in the exo orientation as shown.

Unlike the aldehyde **6**, the aldehyde **26** undergoes cycloaddition with the free base *N*-methyl glycine ethyl ester. The aldehyde **26** also undergoes cycloaddition in the presence of other amines. Thus, condensation of the aldehyde **26** and glycine ethyl ester, followed by heating in a sealed tube at 130 °C, gave the tricyclic product **28** as predominantly one diastereomer (Scheme 9). The stereochemistry of the major product is assigned with the ethyl ester group in the endo orientation, as *N*-methylation of **28** gives a product that is isomeric and not identical with the cycloadduct **27** (the endo product is the major product from the dipolar cycloaddition reaction of glycine ethyl ester and the aldehyde **4**).[10,16] Condensation of the aldehyde **26** and *N*-allyl glycine ethyl ester gave a separable mixture of cycloadducts **29** and **30** (Scheme 10). The major product was assigned the stereoisomer **29** on the basis of the following evidence. Deallylation of the major product **29** with palladium(0)[17] gave the tricyclic compound **31** (Scheme 11), which was different from the cycloadduct **28** (but corresponded to the very small amount of the minor diastereomer formed in the reaction

(16) See also the Supporting Information.
(17) Lemaire-Audoire, S.; Savignac, M.; Genêt, J. P.; Bernard, J.-M. *Tetrahedron Lett.* **1995**, *36*, 1267−1270.

of the aldehyde **26** and glycine ethyl ester). Treatment of compound **31** with iodomethane gave the product **27**. Hence we were certain that the major stereoisomer in the cycloaddition reaction with *N*-allyl glycine ethyl ester was the desired compound **29**, with the ethyl ester group in the exo orientation.

The aldehyde **26**, with a dimethyl acetal protecting group, has therefore allowed the preparation of both the exo and endo diastereomers of the cycloadduct (**28** and **31**). Such *N*-unsubstituted compounds were not accessible with the dithiane protecting group (from aldehyde **6**). The formation of the desired stereoisomer of the *N*-unsubstituted tricyclic compound **31** opens the way for further functionalization on the nitrogen atom of ring C, to prepare substrates with which to effect cyclization to give the eight-membered ring E. Studies along these lines are in progress and will be reported shortly.

Conclusion

An efficient route to the tricyclic ABC ring system of manzamine A has been accomplished. The synthesis starts from arecoline and makes use of the Claisen rearrangement and the intramolecular [3+2] cycloaddition reaction of an azomethine ylide as key steps. The cycloaddition reaction sets up rings B and C in a single step and its stereoselectivity has been determined for a variety of substituted azomethine ylides. The chemistry provides the desired cis-fused AB and BC ring systems in the tricyclic core, with the formation of either the endo or exo stereoisomer, depending on the choice of amine for the cycloaddition reaction. As this methodology gives access to the *N*-unsubstituted pyrrolidine ring C, further functionalization is possible, for example, toward the natural product manzamine A itself.

Experimental Section

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated. Diethyl ether and THF were distilled from sodium/benzophenone. Dichloromethane and hexamethylphosphoramide (HMPA) were distilled from CaH_2. Diisopropylamine was distilled from KOH. Light petroleum refers to the boiling point range 40−60 °C and was distilled prior to use. Chromatography was performed with Merck Kieselgel 60H silica (230−400 mesh).

NMR spectra chemical shifts (δ) are in ppm and coupling constants J are in hertz. NMR peak multiplicities are given the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

Methyl *N*-(*tert*-Butoxycarbonyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (9). K_2CO_3 (18.3 g, 133 mmol) was added to arecoline hydrobromide (25 g, 106 mmol) in water (60 mL). After 30 min, the mixture was extracted with Et_2O (4 × 100 mL), the organic layers were dried ($MgSO_4$) and evaporated, and the resulting oil was dissolved in toluene (120 mL). 1-Chloroethyl chloroformate (14 mL, 128 mmol) was added slowly and the mixture was heated under reflux. After 16 h, HCl (100 mL, 0.1 M) was added and the mixture was extracted with Et_2O. The organic layers were dried ($MgSO_4$) and evaporated. The resulting carbamate was dissolved in MeOH (100 mL) and heated under reflux. After 2 h, the solvent was evaporated and the resulting amine **8**[12] was dissolved in CH_2Cl_2 (150 mL) and cooled to 0 °C. Et_3N (16.5 mL, 118 mmol) and di-*tert*-butyl dicarbonate (31.7 g, 145 mmol) were added. After 24 h, HCl (100 mL, 1 M) was added and the mixture was extracted with CH_2Cl_2. The organic layers were washed with saturated $NaHCO_3$, dried ($MgSO_4$), evaporated, and purified by column chromatography, eluting with light petroleum−EtOAc (9:1), to give the carbamate **9**[18] (20 g, 83 mmol, 78%) as an oil that crystallizes at low temperature: mp 29−31 °C; ν_{max} (film)/cm^{-1} 1720, 1700, 1655; δ_H (400 MHz, $CDCl_3$) corresponds to literature[18] values; δ_C (100 MHz, $CDCl_3$) 25.5, 28.4, 39.0−39.9 (br), 42.6 (br), 51.7, 80.0, 128.1 (br), 137.9 (br), 154.8, 165.8 (found M$^+$, 241.1317, $C_{12}H_{19}NO_4$ requires M 241.1314). Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81. Found: C, 60.04; H, 8.30; N, 5.77.

***N*-(*tert*-Butoxycarbonyl)-3-hydroxymethyl-1,2,5,6-tetrahydropyridine (10).** Diisobutylaluminum hydride (100 mL, 100 mmol, 1 M in hexanes) was added slowly to the ester **9** (8.6 g, 35.7 mmol) in dry Et_2O (160 mL) under nitrogen at −70 °C. After 50 min, MeOH (10 mL) was added and the mixture was allowed to warm to room temperature. A solution of sodium potassium tartrate (100 mL, 1 M) was added and the mixture was extracted with EtOAc. The organic layers were dried ($MgSO_4$), evaporated, and purified by column chromatography, eluting with light petroleum−EtOAc (3:2), to give the alcohol **10** (6.5 g, 30.5 mmol, 85%) as an oil: ν_{max} (film)/cm^{-1} 3450, 1695; δ_H (400 MHz, $CDCl_3$) 1.39 (9H, s), 2.02−2.15 (2H, m), 2.80−3.25 (1H, br s), 3.35−3.40 (2H, m), 3.82 (2H, s), 3.96 (2H, s), 5.73 (1H, br s); δ_C (100 MHz, $CDCl_3$) 24.7, 28.4, 39.5−40.8 (br), 43.7 (br), 64.7, 79.7, 121.2 (br), 135.5 (br), 155.1 (found MH$^+$ 214.1437, $C_{11}H_{20}NO_3$ requires MH 214.1443).

Ethyl [4-(1-*tert*-Butoxycarbonyl)(3-methylenyl)piperidinyl]ethanoate (11). Triethylorthoacetate (32 mL, 175 mmol), 2,4-dinitrophenol (1.6 g, 8.7 mmol), and the alcohol **10** (7.4 g, 34.7 mmol) were heated in xylene (15 mL) with use of a Dean−Stark trap. After 48 h, NaOH (30 mL, 0.5 M) was added and the mixture was extracted with Et_2O. The organic layers were washed with NaOH (0.5 M) and brine, dried ($MgSO_4$), evaporated, and purified by column chromatography, eluting with hexanes−EtOAc (9:1), to give the ester **11** (6.2 g, 21.9 mmol, 63%) as an oil: ν_{max} (film)/cm^{-1} 1735, 1695, 1655; δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, J = 7.2 Hz), 1.25−1.31 (1H, m), 1.44 (9H, s), 1.76−1.85 (1H, m), 2.30 (1H, dd, J = 14.9, 7.4 Hz), 2.56−2.73 (2H, m), 3.02−3.13 (1H, m), 3.51 (1H, d, J = 13.9 Hz), 3.83−3.92 (1H, m), 4.12 (2H, q, J = 7.2 Hz), 4.20−4.33 (1H, m), 4.69 (1H, s), 4.89 (1H, br s); δ_C (100 MHz, $CDCl_3$) 14.2, 28.4, 32.4, 37.3, 37.7, 43.0, 50.8 (br), 60.4, 79.5, 108.7, 144.9, 154.6, 172.3 (found MH$^+$ 284.1864, $C_{15}H_{26}NO_4$ requires MH 284.1862).

[4-(1-*tert*-Butoxycarbonyl)(3-methylenyl)piperidinyl]-ethanal (12). The alcohol **10** (3.2 g, 15 mmol), xylene (15 mL), $Hg(OAc)_2$ (478 mg, 1.5 mmol), and freshly distilled ethyl vinyl ether (20 mL, 0.21 mol) were heated in a sealed tube at 135 °C. After 5 d, the solvent was evaporated and the residue was purified by column chromatography, eluting with light petroleum−EtOAc (4:1), to give the aldehyde **12** (2.83 g, 11.8 mmol, 79%) as an oil that crystallizes at low temperature: mp 53−55 °C; ν_{max} ($CHCl_3$)/cm^{-1} 1725, 1695, 1655; δ_H (400 MHz, $CDCl_3$) 1.24−1.40 (1H, m), 1.45 (9H, s), 1.75−1.84 (1H, m), 2.37−2.50 (1H, m), 2.65−2.83 (2H, m), 3.02−3.13 (1H, m), 3.51 (1H, d, J = 13.9 Hz), 3.85−3.96 (1H, m), 4.20−4.35 (1H, m), 4.66 (1H, s), 4.93 (1H, br s), 9.78 (1H, s); δ_C (100 MHz, $CDCl_3$) 28.4, 32.6, 35.5, 43.1, 46.0, 50.7 (br), 79.7, 109.3, 144.6, 154.6, 201.2 (found MH$^+$ 240.1597, $C_{13}H_{22}NO_3$ requires MH 240.1599). Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.25; H, 8.84; N, 5.85. Found: C, 64.91; H, 9.09; N, 5.63.

***N*-(*tert*-Butoxycarbonyl)-4-(2′-hydroxyethyl)-3-methylenepiperidine (13).** Lithium aluminum hydride (650 mg, 17.1 mmol) was added to the aldehyde **12** (8.2 g, 34.3 mmol) in dry THF (200 mL) at 0 °C. After 15 min, water (2.5 mL), NaOH (2.5 mL, 4 M), and water (7.5 mL) were added. After 20 min, the mixture was filtered through Celite, washed with EtOAc, evaporated, and purified by column chromatography, eluting

(18) Showell, G. A.; Gibbons, T. L.; Kneen, C. O.; MacLeod, A. M.; Merchant, K.; Saunders: J.; Freedman, S. B.; Patel, S.; Baker, R. *J. Med. Chem.* **1991**, *34*, 1086−1094.

with light petroleum−EtOAc (3:2), to give the alcohol **13** (8.1 g, 33.6 mmol, 98%) as an oil: ν_{max} (film)/cm^{-1} 3430, 1695, 1675; δ_H (400 MHz, $CDCl_3$) 1.22−1.35 (1H, m), 1.39 (9H, s), 1.48−1.62 (1H, m), 1.74−1.85 (1H, m), 1.85−1.98 (1H, m), 2.26−2.33 (1H, m), 2.30−2.56 (1H, br s), 3.13−3.24 (1H, m), 3.55−3.74 (4H, m), 4.03 (1H, d, J = 6.4 Hz), 4.72 (1H, s), 4.86 (1H, br s); δ_C (100 MHz, $CDCl_3$) 28.4, 34.0, 37.1, 37.4, 42.2 (br), 49.8 (br), 60.2, 79.5, 109.2, 145.8, 154.7 (found M$^+$ 241.1674, $C_{13}H_{23}NO_3$ requires M 241.1678). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.78; H, 10.06; N, 5.78.

Alternatively, lithium aluminum hydride (1.5 g, 39.5 mmol) was added to the ester **11** (11.14 g, 39.3 mmol) in dry THF (200 mL) at 0 °C. The mixture was allowed to warm to room temperature for 2 h. After the mixture was cooled to 0 °C, water (5 mL), NaOH (5 mL, 4 M), and water (15 mL) were added. After 20 min, the mixture was filtered through Celite, washed with EtOAc, evaporated, and purified as above to give the alcohol **13** (8.5 g, 35.2 mmol, 89%) as an oil with data as above.

***N*-(*tert*-Butoxycarbonyl)-4-(2′-iodoethyl)-3-methylenepiperidine (14).** To the alcohol **13** (8.2 g, 34 mmol) in THF (180 mL) was added successively Ph_3P (10 g, 38.1 mmol), imidazole (2.6 g, 38.2 mmol), and iodine (9.67 g, 38.1 mmol) at room temperature. After 2 h, the mixture was filtered through Celite, washed with EtOAc, evaporated, and purified by column chromatography, eluting with light petroleum−EtOAc (92:8), to give the iodide (9.7 g, 27.6 mmol, 81%) as an oil: ν_{max} (film)/cm^{-1} 1695, 1650; δ_H (400 MHz, $CDCl_3$) 1.25−1.37 (1H, m), 1.43 (9H, s), 1.76−1.88 (2H, m), 2.09−2.22 (1H, m), 2.27−2.38 (1H, m), 3.19 (2H, t, J = 7.1 Hz), 3.22−3.32 (1H, m), 3.58−3.72 (1H, m), 3.69 (1H, d, J = 14.0 Hz), 4.00 (1H, d, J = 14.0 Hz), 4.77 (1H, s), 4.93 (1H, br s); δ_C (100 MHz, $CDCl_3$) 4.2, 28.4, 31.4, 35.1, 41.2, 42.2 (br), 49.6 (br), 79.6, 109.9 (br), 144.3, 154.6 (found M$^+$ 351.0695, $C_{13}H_{22}INO_2$ requires M 351.0695). Anal. Calcd for $C_{13}H_{22}INO_2$: C, 44.46; H, 6.31; N, 3.99. Found: C, 44.32; H, 6.46; N, 3.85.

Ethyl 4-[4′-(1′-*tert*-Butoxycarbonyl)(3′-methylenyl)piperidinyl]-2-(propylenedithioketal)butanoate (16). *n*-BuLi (14.4 mL, 36 mmol, 2.5 M in hexanes) was added to ethyl 1,3-dithiane-2-carboxylate **15** (5.68 mL, 36 mmol) in dry THF (90 mL) and dry HMPA (22 mL) under argon at −60 °C. The mixture was stirred for 1.5 h at −40 °C, then the iodide **14** (9.7 g, 27.6 mmol) in dry THF (30 mL) was added. The mixture was allowed to warm slowly to room temperature for 16 h. Water was added and the mixture was extracted into EtOAc. The organic layers were washed with water, dried ($MgSO_4$), evaporated, and purified by column chromatography, eluting with light petroleum−EtOAc (9:1), to give the ester **16** (11 g, 26.5 mmol, 96%) as an oil: ν_{max} (film)/cm^{-1} 1720, 1695, 1650; δ_H (400 MHz, $CDCl_3$) 1.31 (3H, t, J = 7.1 Hz), 1.27−1.41 (1H, m), 1.43 (9H, s), 1.48−1.62 (1H, m), 1.75−1.93 (3H, m), 1.96−2.07 (2H, m), 2.09−2.21 (2H, m), 2.61−2.69 (2H, m), 3.19−3.36 (3H, m), 3.57−3.68 (1H, m), 3.66 (1H, d, J = 13.9 Hz), 4.00 (1H, d, J = 13.9 Hz), 4.24 (2H, q, J = 7.1 Hz), 4.77 (1H, s), 4.89 (1H, br s); δ_C (100 MHz, $CDCl_3$) 14.2, 24.7, 26.0, 27.9, 28.3, 32.2, 36.7, 41.1, 42.1, 49.8 (br), 52.2, 61.8, 79.4, 109.7, 145.2, 154.6, 170.9 (found MH$^+$ 416.1934, $C_{20}H_{34}NO_4S_2$ requires MH 416.1929). Anal. Calcd for $C_{20}H_{33}NO_4S_2$: C, 57.80; H, 8.00; N, 3.37. Found: C, 57.41; H, 8.26; N, 3.27.

4-[4′-(1′-*tert*-Butoxycarbonyl)(3′-methylenyl)piperidinyl]-2-(propylenedithioketal)butan-1-ol (17). $LiAlH_4$ (915 mg, 24.1 mmol) was added to the ester **16** (11.6 g, 24.1 mmol) in dry THF (250 mL) at 0 °C. The mixture was allowed to warm to room temperature for 30 min. After the mixture was cooled to 0 °C, water (3 mL), NaOH (3 mL, 4 M), and water (9 mL) were added. After 20 min, the mixture was filtered through Celite, washed with EtOAc, evaporated, and purified by column chromatography, eluting with light petroleum−EtOAc (3:2), to give the alcohol **17** (8.5 g, 22.7 mmol, 94%) as an oil: ν_{max} (film)/cm^{-1} 3455, 1690; δ_H (400 MHz, $CDCl_3$) 1.30−1.42 (1H, m), 1.44 (9H, s), 1.43−1.58 (1H, m), 1.72−1.91 (5H, m), 2.02−2.15 (3H, m), 2.55−2.65 (2H, m), 2.88−2.98 (2H, m), 3.19−3.30 (1H, m), 3.61−3.71 (1H, m), 3.66 (1H, d, J = 13.9 Hz), 3.76 (2H, d, J = 4.3 Hz), 4.03 (1H, d, J = 13.9 Hz), 4.78 (1H, s), 4.91 (1H, br s); δ_C (100 MHz, $CDCl_3$) 24.8, 25.1, 25.7, 25.8, 28.4, 32.3, 35.5, 41.1, 42.0, 49.6 (br), 54.4, 63.3, 79.4, 109.7, 145.3, 154.7 (found MH$^+$ 374.1826, $C_{18}H_{32}NO_3S_2$ requires MH 374.1823).

4-[4′-(1′-*tert*-Butoxycarbonyl)(3′-methylenyl)piperidinyl]-2-(propylenedithioketal)butanal (6). Dimethyl sulfoxide (3 mL, 42.3 mmol) was added dropwise to oxalyl chloride (1.7 mL, 19.5 mmol) in CH_2Cl_2 (40 mL) at −70 °C. After 20 min, the alcohol **17** (3.15 g, 8.4 mmol) in CH_2Cl_2 (10 mL) was added slowly. After 50 min, Et_3N (6.1 mL, 43.8 mmol) was added and the mixture was allowed to warm to room temperature. Water was added and the mixture was extracted with CH_2Cl_2. The organic layers were dried ($MgSO_4$), evaporated, and purified by column chromatography, eluting with light petroleum−EtOAc (85:15), to give the aldehyde (2.67 g, 7.2 mmol, 85%) as an oil: ν_{max} (film)/cm^{-1} 1715,1695, 1655; δ_H (400 MHz, $CDCl_3$) 1.28−1.43 (1H, m), 1.44 (9H, s), 1.43−1.69 (1H, m), 1.74−1.90 (5H, m), 2.06−2.17 (2H, m), 2.63 (2H, dt, J = 14.5, 1.1 Hz), 3.02 (2H, td, J = 14.5, 3.0 Hz), 3.22−3.27 (1H, m), 3.60−3.70 (1H, m), 3.69 (1H, d, J = 14.0 Hz), 4.00 (1H, d, J = 14.0 Hz), 4.75 (1H, s), 4.93 (1H, br s), 9.04 (1H, s); δ_C (100 MHz, $CDCl_3$) 24.4, 25.3, 26.7, 28.4, 32.2, 33.6, 41.0, 42.0, 49.6 (br), 58.0, 79.5, 110.0, 144.8, 154.6, 189.3 (found MH$^+$ 372.1668, $C_{18}H_{30}NO_3S_2$ requires MH 372.1667). Anal. Calcd for $C_{18}H_{29}NO_3S_2$: C, 58.19; H, 7.87; N, 3.77. Found: C, 58.18; H, 8.21; N, 3.67.

(3*RS*,5*RS*,7*RS*,11*RS*)-Ethyl 1,6-Diaza-1-*tert*-butoxycarbonyl-8-propylenedithioketal-6-methyltricyclo[7.4.0^{3,7}.0^{3,11}]-tridecane-5-carboxylate (18). The aldehyde **6** (2.43 g, 6.5 mmol), dry toluene (40 mL), *N*-methyl glycine ethyl ester hydrochloride (2 g, 13 mmol), and diisopropylethylamine (2.28 mL, 13.1 mmol) were heated with a Dean−Stark trap. After 3 d, the solvent was evaporated and the residue was purified by column chromatography, eluting with light petroleum−EtOAc (4:1), to give the compound (1.36 g, 2.9 mmol, 45%) as needles: mp 140−142 °C; ν_{max} ($CHCl_3$)/cm^{-1} 1735, 1685; δ_H (400 MHz, $CDCl_3$) 1.28 (3H, t, J = 7.0 Hz), 1.29−2.17 (11H, m), 1.41 (9H, s), 2.59 (2H, br t, J = 13.5 Hz), 2.74−2.81 (1H, m), 2.83 (1H, s), 2.86 (3H, s), 2.93 (1H, t, J = 12.5 Hz), 2.97−3.16 (1H, m), 3.27 (1H, t, J = 12.5 Hz), 3.55−3.75 (3H, m), 4.11−4.16 (2H, m); δ_C (100 MHz, $CDCl_3$) 14.3, 22.0, 25.8, 25.9, 26.5, 27.6, 28.4, 29.8, 33.8, 33.9, 38.8, 39.1, 47.1, 50.7, 55.7, 60.0, 65.1, 73.5, 79.3, 155.1, 173.9 (found MH$^+$ 471.2353, $C_{23}H_{39}N_2O_4S_2$ requires MH 471.2351). Anal. Calcd for $C_{23}H_{38}N_2O_4S_2$: C, 58.69; H, 8.14; N, 5.95. Found: C, 58.50; H, 8.30; N, 5.76.

4-[4′-(1′-*tert*-Butoxycarbonyl)(3′-methylenyl)piperidinyl]-2,2-dimethoxybutanal (26). The alcohol **17** (2.75 g, 7.4 mmol) in dry THF (10 mL) was added to a mixture of $AgNO_3$ (5.65 g, 33.3 mmol), 2,4,6-collidine (7.8 mL, 59 mmol), and *N*-chlorosuccinimide (3.95 g, 29.6 mmol) in dry MeOH (60 mL) and dry THF (60 mL) at 0 °C. After 90 min, saturated $Na_2S_2O_3$, saturated Na_2CO_3, and brine were added successively. The mixture was filtered through Celite and was washed with hexane−CH_2Cl_2 (1:1). The organic and aqueous layers were separated and the aqueous layer was extracted with hexane−CH_2Cl_2 (1:1). The combined organic layers were dried ($MgSO_4$), evaporated, and purified by column chromatography, eluting with light petroleum−EtOAc (1:1), to give the alcohol **25** as a mixture with 2,4,6-collidine.

In the same way as the aldehyde **6**, dimethyl sulfoxide (2.5 mL, 35.2 mmol), oxalyl chloride (1.42 mL, 16.3 mmol), this mixture containing the alcohol **25**, then Et_3N (5.2 mL, 37.3 mmol) gave, after purification by column chromatography (× 2), eluting with light petroleum−EtOAc (7:3), the aldehyde **26** (1.25 g, 3.8 mmol, 51%) as an oil: ν_{max} (film)/cm^{-1} 1750, 1695, 1655; δ_H (400 MHz, $CDCl_3$) 1.15−1.27 (2H, m), 1.38 (9H, s), 1.45−1.51 (1H, m), 1.70−1.77 (3H, m), 2.00−2.05 (1H, m), 3.14−3.26 (1H, m), 3.22 (3H, s), 3.23 (3H, s), 3.50−3.65 (1H, m), 3.62 (1H, d, J = 13.9 Hz), 3.93 (1H, d, J = 13.9 Hz), 4.66

(1H, s), 4.85 (1H, br s), 9.42 (1H, s); δ_C (100 MHz, $CDCl_3$) 24.1, 28.4, 29.3, 32.0, 40.8, 42.0 (br), 48.7−50.2 (br), 49.6, 79.5, 102.2, 109.8, 145.0, 154.6, 200.2 (found MH^+ 328.2126, $C_{17}H_{30}NO_5$ requires MH 328.2124). Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 61.99; H, 9.19; N, 4.15.

(3*RS*,5*RS*,7*RS*,11*RS*)-Ethyl 1,6-Diaza-1-*tert*-butoxycarbonyl-8,8-dimethoxy-6-methyltricyclo[7.4.0^{3,7}.0^{3,11}]-tridecane-5-carboxylate (27). The aldehyde **26** (180 mg, 0.55 mmol), dry toluene (5 mL), and *N*-methyl glycine ethyl ester (130 mg, 1.1 mmol) were heated with use of a Dean−Stark trap. After 16 h, the mixture was evaporated and purified by column chromatography, eluting with light petroleum−EtOAc (4:1), to give the ester **27** (132 mg, 0.31 mmol, 56%) as an oil: ν_{max} (film)/cm^{-1} 1730, 1690; δ_H (400 MHz, $CDCl_3$) 1.17−1.32 (5H, m), 1.40 (9H, s), 1.61−1.80 (5H, m), 1.82−1.95 (1H, m), 2.14 (1H, dd, J = 13.3, 9.0 Hz), 2.51 (3H, s), 2.64−2.81 (1H, m), 3.07 (1H, s), 3.14 (3H, s), 3.19 (3H, s), 3.33−3.60 (2H, m), 3.71 (1H, dd, J = 9.0, 6.0 Hz), 3.82−4.00 (1H, m), 4.05−4.18 (2H, m); δ_C (100 MHz, $CDCl_3$) 14.4, 24.5, 27.2, 27.3, 28.4, 34.9, 35.1, 38.3, 39.6, 46.6, 46.8, 47.8, 49.1, 60.0, 64.0, 64.4, 79.0, 101.8, 154.6, 174.7 (found MH^+ 427.2805, $C_{22}H_{39}N_2O_6$ requires MH 427.2808). Anal. Calcd for $C_{22}H_{38}N_2O_6$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.70; H, 9.30; N, 6.36.

Alternatively, HgO (737 mg, 3.4 mmol) was added to the ester **18** (400 mg, 0.85 mmol) in dry MeOH (25 mL) at 65 °C. A solution of $HgCl_2$ (693 mg, 2.55 mmol) in dry MeOH (2 mL) was added dropwise. After 25 min the hot mixture was filtered, washed with MeOH, and evaporated. CH_2Cl_2 (25 mL) was added and the mixture was filtered. The filtrate was washed with aqueous KI (2 × 20 mL, 10%), water (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$), evaporated, and purified by column chromatography, as above, to give the ester **27** (290 mg, 0.68 mmol, 80%) with data as above.

Alternatively, K_2CO_3 (188 mg, 1.36 mmol) and methyl iodide (0.105 mL, 1.68 mmol) were added to the amine **31** (70 mg, 0.17 mmol) in dry DMF (3 mL). The mixture was heated at 45 °C for 2 h. Water was added and the mixture was extracted with EtOAc. The organic layers were dried ($MgSO_4$), evaporated, and purified by column chromatography, as above, to give the ester **27** (52 mg, 0.12 mmol, 71%) with data as above.

(3*RS*,5*SR*,7*RS*,11*RS*)-Ethyl 1,6-Diaza-1-*tert*-butoxycarbonyl-8,8-dimethoxytricyclo[7.4.0.^{3,7}0^{3,11}]tridecane-5-carboxylate (28). The aldehyde **26** (590 mg, 1.8 mmol) in dry toluene (5 mL) and glycine ethyl ester (370 mg, 3.6 mmol) were heated under reflux with use of a Dean−Stark trap. After 16 h, the solvent was evaporated. The resulting imine was dissolved in dry toluene (3.5 mL), placed in a sealed tube (90 × 15 mm), and heated at 130 °C. After 4 d, the solvent was evaporated and the residue was purified by column chromatography, eluting with light petroleum−EtOAc (3:2), to give the amine **28** (383 mg, 0.93 mmol, 52%) as an oil (as a mixture with another diastereoisomer, ratio >9:1): ν_{max} (film)/cm^{-1} 3355, 1730, 1690; δ_H (400 MHz, C_6D_6, 75 °C) 1.00−1.17 (5H, m), 1.55 (9H, s), 1.62−1.72 (1H, m), 1.77−1.99 (4H, m), 2.26 (1H, dd, J = 13.6, 10.7 Hz), 2.46 (1H, dd, J = 13.6, 4.1 Hz), 2.65−2.79 (1H, m), 2.92 (1H, s), 3.04 (3H, s), 3.17 (3H, s), 3.43 (1H, d, J = 13.3 Hz), 3.73 (1H, dd, J = 10.7, 4.1 Hz), 3.83−3.92 (1H, m), 3.99−4.15 (3H, m); δ_C (100 MHz, C_6D_6, 75 °C) 13.8, 24.0, 27.3, 27.7, 28.2, 34.3, 39.9, 40.0, 45.0, 46.7, 47.2, 47.9, 56.8, 60.2, 64.9, 78.4, 101.1, 154.4, 174.3 (found MH^+ 413.2648, $C_{21}H_{37}N_2O_6$ requires MH 413.2651). Anal. Calcd for $C_{21}H_{36}N_2O_6$: C, 61.14; H, 8.80; N, 6.79. Found: C, 60.80; H, 8.98; N, 6.61.

(3*RS*,5*RS*,7*RS*,11*RS*)-Ethyl 1,6-Diaza-1-*tert*-butoxycarbonyl-8,8-dimethoxy-6-allyltricyclo[7.4.0^{3,7}.0^{3,11}]tridecane-5-carboxylate (29). In the same way as the amine **27**, the aldehyde **26** (1.0 g, 3.05 mmol) and *N*-allyl glycine ethyl ester (875 mg, 6.12 mmol) gave, after purification by column chromatography, eluting with light petroleum−EtOAc (9:1), the amine **29** (595 mg, 1.31 mmol, 43%) as an oil: ν_{max} (film)/cm^{-1} 1735, 1695; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, J = 7.1 Hz), 1.25−1.32 (2H, m), 1.41 (9H, s), 1.55−1.95 (6H, m), 2.21 (1H, dd, J = 13.3, 9.3 Hz), 2.71−2.83 (1H, m), 3.15 (3H, s), 3.21 (3H, s), 3.23 (1H, s), 3.37 (1H, dd, J = 13.7, 8.5 Hz), 3.42−3.56 (2H, m), 3.80 (1H, dd, J = 9.3, 6.0 Hz), 3.86−3.98 (1H, m), 4.04−4.17 (3H, m), 4.98 (1H, d, J = 10.4 Hz), 5.07 (1H, d, J = 17.2 Hz), 5.69−5.82 (1H, m); δ_C (100 MHz, $CDCl_3$) 14.3, 24.5, 27.2, 27.4, 28.5, 34.6 (br), 38.5, 39.7 (br), 46.4, 46.7, 47.6, 49.3, 49.7, 59.9, 59.9, 63.0, 79.0, 101.9, 115.8, 137.2, 154.7, 175.0 (found MH^+ 453.2974, $C_{24}H_{41}N_2O_6$ requires MH 453.2965) and an inseparable mixture (∼4:1) of the amine **30** and the aldehyde **26** (102 mg, equating to ∼6% yield of the minor diastereomer **30**) as an oil.

(3*RS*,5*RS*,7*RS*,11*RS*)-Ethyl 1,6-Diaza-1-*tert*-butoxycarbonyl-8,8-dimethoxytricyclo[7.4.0^{3,7}.0^{3,11}]tridecane-5-carboxylate (31). Bis(dibenzylidene-acetone)palladium (390 mg, 0.68 mmol) was added to 1,4-bis(diphenylphosphino)butane (290 mg, 0.68 mmol) in dry THF (15 mL) under nitrogen at room temperature. After 15 min, the amine **29** (2.04 g, 4.51 mmol) in dry THF (50 mL) and thiosalicylic acid (765 mg, 4.96 mmol) were added. After 3 h, saturated $NaHCO_3$ was added and the mixture was extracted with EtOAc. The organic layers were dried ($MgSO_4$), evaporated, and purified by column chromatography, eluting with light petroleum−EtOAc (3:2), to give the amine **31** (1.60 g, 3.88 mmol, 86%) as an oil: ν_{max} (film)/cm^{-1} 3365, 1735, 1695; δ_H (400 MHz, C_6D_6, 75 °C) 1.04−1.11 (5H, m), 1.55 (9H, s), 1.65−1.77 (2H, m), 1.80−1.95 (2H, m), 2.00−2.08 (1H, m), 2.14 (1H, dd, J = 13.4, 7.3 Hz), 2.42 (1H, dd, J = 13.4, 8.8 Hz), 2.66−2.77 (1H, m), 3.04 (3H, s), 3.21 (1H, s), 3.22 (3H, s), 3.51 (1H, d, J = 13.7 Hz), 3.81 (1H, dd, J = 8.8, 7.3 Hz), 3.80−3.92 (1H, m), 3.97−4.22 (3H, m); δ_C (100 MHz, C_6D_6, 75 °C) 13.9, 24.3, 27.3, 27.4, 28.3, 34.2, 40.0, 41.0, 45.6, 46.7, 47.1, 48.4, 55.9, 60.3, 63.1, 78.4, 101.4, 154.4, 175.6 (found MH^+ 413.2645, $C_{21}H_{37}N_2O_6$ requires MH 413.2651).

Acknowledgment. We are grateful to the EPSRC for funding (to K.M.C. and R.R.), Zeneca Pharmaceuticals (now AstraZeneca) for a CASE Studentship (to K.M.C.), and the Spanish Government (Ministerio de Educación y Cultura) for a postdoctoral fellowship (to J.-C.F.). Alan B. Treacy is thanked for initial studies. The EPSRC mass spectrometry service at the University of Wales, Swansea and the EPSRC X-ray service at the University of Southampton are thanked.

Note Added after ASAP. Reference 7c was added after the version posted 7/27/2002; the new version was posted 7/31/2002.

Supporting Information Available: Experimental details and data for compounds **21**−**23** and **30** and ^{13}C NMR spectra of compounds **10**, **11**, **17**, **21**−**23**, **29**, and **31**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016376S