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Synthetic Studies Towards Novel Tetracyclic Lycopodium Alkaloids: A Synthesis of Deoxymagellaninone

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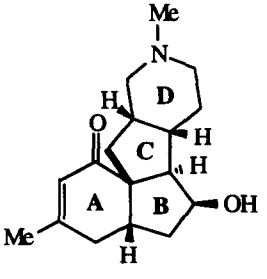
Abstract: A short, novel, linear triquinane-based strategy, directed towards the synthesis of complex tetracyclic alkaloids of paniculatine and magellanine-type, and culminating in the synthesis of deoxymagellaninone **32** is delineated. The cornerstone of our approach was the utilization of the 'carbocycle-heterocycle equivalency' stratagem to generate the N-methylpiperidine ring-D from a cyclopentene precursor, e.g. **35**→**38**. The six-membered ring-A present in the natural products was constructed either through cationic enone-olefin cyclization (**25**→**26**) or intramolecular Michael addition (**34**→**35**) protocols. Overall, the synthetic effort outlined here is notable for its brevity, conceptual simplicity and desirable levels of regio- and stereoselective control in various steps.

Key words: Michael reaction; Piperidines; Cyclopentenones; Alkaloids.

Among the innumerable sources of alkaloid natural products, the *Lycopodiaceae* family, is one of the largest and many novel compounds with diverse skeletal features and broad ranging biological activity profile continue to be isolated from this source.[1] In recent years, collaborative efforts between organic chemists in Chile and Canada have led to the isolation and structure determination of the structurally complex alkaloids magellanine **1** and magellanione **2** (isolated from *L. magellanicum*)[2a,b] as well as the closely related paniculatine **3** (isolated from *L.paniculatum*),[2c] and are relatively new and rare members of the Lycopodium family.[2] These alkaloids **1-3** are characterized by a structurally unique tetracyclic framework built around a diquinane core (rings B,C), embellished with five stereogenic centers and extensive functionalization, and hold considerable synthetic appeal. Not surprisingly, several research groups have been drawn towards the synthesis of these novel structural types.[3-6]



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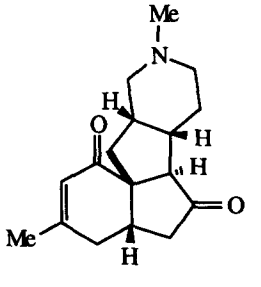

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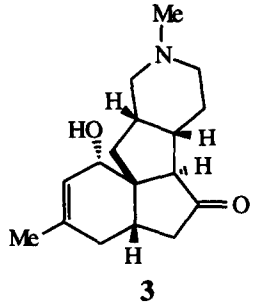

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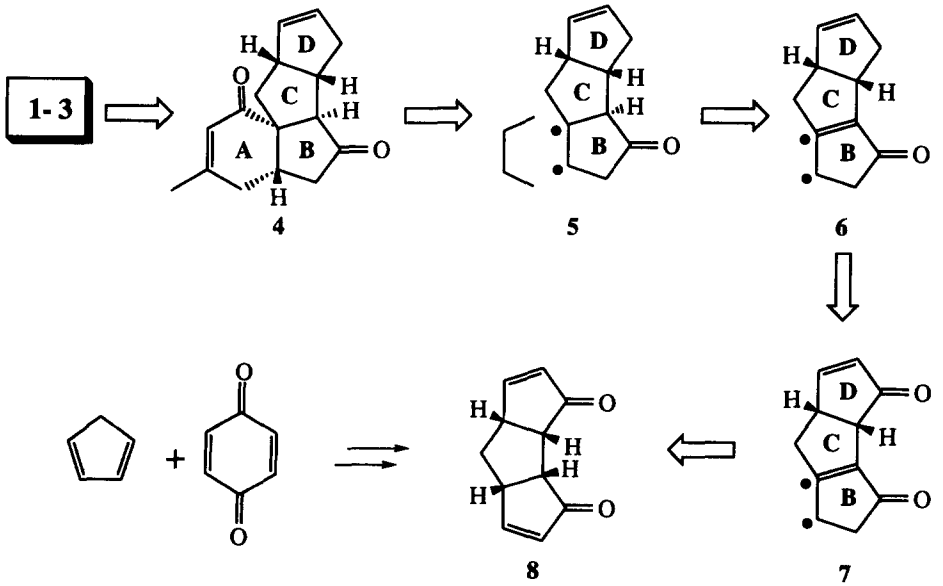
PII: S0040-4020(98)00421-9

Sometime back, we were the first to report the successful synthesis of the complete tetracyclic skeleton present in these alkaloids.[3] More recently, Overman *et al.*[5] successfully completed the total synthesis of (-)-magellanine **1** and (+)-magellanione **2** employing stannic chloride catalyzed Prins-pinacol rearrangement as the pivotal step. Concurrently, Paquette *et al.*[6] have reported the total synthesis of racemic **1** and **2** following a different strategy. Herein, we present a full account[7] of our studies towards the synthesis of **1-3** leading to a synthesis of deoxymagellaninone.

Synthetic plan

The main challenge in the synthesis of complex structures **1-3** is the generation of the tetracarbocyclic skeleton, control of stereochemistry at the five contiguous stereocenters and management of functionalities. Our synthetic plan towards **1-3** evolved around the recognition that a carbocyclic cyclopentene ring can be regarded as an equivalent of the heterocyclic piperidine ring. Thus, the N-methylpiperidine substructure (ring D) present in these alkaloids **1-3** can be replaced by a cyclopentene ring as in **4**. This operation revealed the dominant presence of the linearly-fused triquinane moiety, in a latent form, in the framework of these alkaloids and also provided an important strategic lead towards their synthesis. Following this lead, a retrosynthetic plan emerged and is depicted in Scheme 1. Dismantling the ring 'A' in **4**

Scheme 1



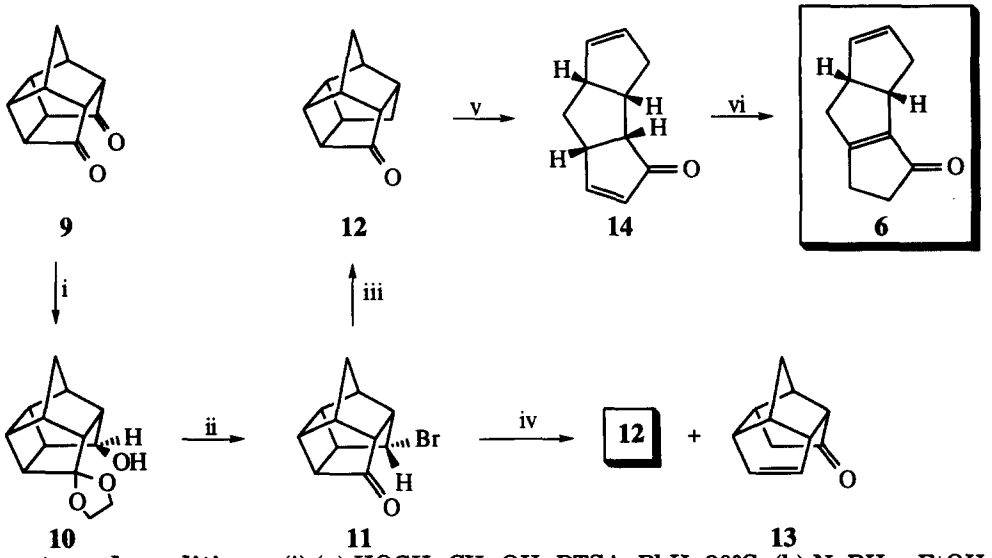
led to the readily identifiable triquinane structure **5**. Further, the structure **5** can be expressed in terms of **6** with two built-in stereocenters and a diquinane moiety (B & C rings), common to all the three alkaloids. The precursor **6** can in turn be traced to the abundantly available triquinane bis-enone **8** *via* **7** through functional group adjustments. Identification of **8** as the main synthon for **1-3** was a very promising outcome as previous contributions from our laboratory have firmly established a three step, high yielding photo-thermal metathesis sequence to it from 1,3-cyclopentadiene and *p*-benzoquinone.[8] Our synthetic strategy to **1-3**, revealed through the retrosynthetic analysis shown in Scheme 1, envisaged three subgoals, namely, efficient acquisition of the triquinane precursor **6**, annulation of the six-membered ring

'A' with required stereochemistry and generation of the N-methylpiperidine ring 'D' employing the 'carbocycle-heterocycle equivalency' concept.

Acquisition of the key triquinane synthon 6

To begin with, we had to ensure ready and abundant access to the key tricyclic synthon **6**. Our first approach was from the easily available Cookson's pentacyclic dione **9**,[9] Scheme 2. The dione **9** was monoprotected to furnish the keto-ketal which was reduced to the corresponding *endo*-hydoxy ketal **10**. On further treatment with aq.HBr, **10** underwent bromination and deketalisation to afford the *exo*-bromide **11**.[10a] Reductive debromination using Li-liq.NH_3 gave a mixture of alcohols which on reoxidation with PCC furnished the monoketone **12** (13%) and the elimination product **13**[8] (8%). Separation of **12** from the co-product **13** was cumbersome and required extensive chromatographic separation. The problem was circumvented through reketalisation of **11** followed by reductive debromination and deprotection sequence to afford **12** in 37% yield.[10b] A thermal [2+2]-cycloreversion in **12** under

Scheme 2



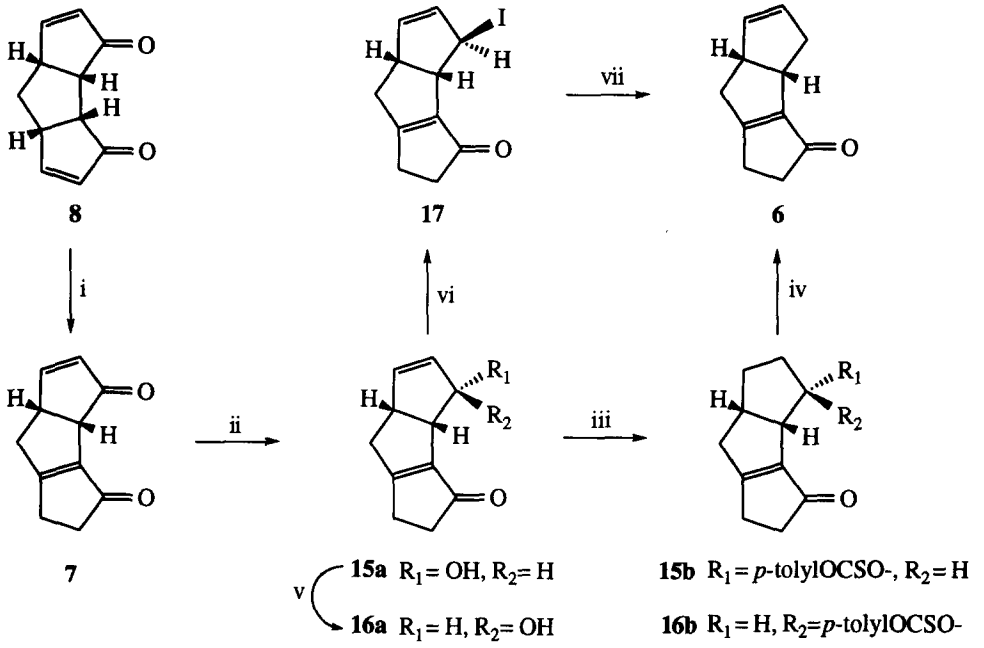
Reagents and conditions: (i) (a) $HOCH_2CH_2OH$, PTSA, PhH, 90°C, (b) $NaBH_4$, EtOH, RT, (ii) 48% aq.HBr, 80°C; (iii) (a) $HOCH_2CH_2OH$, PTSA, PhH, 90°C, (b) Li-liq.NH_3, - 50°C, (c) 20% HCl, THF, RT; (iv) (a) Li- liq.NH_3, -78°C, (b) PCC, DCM, RT; (v) 640°C, 0.3 mm, quartz tube; (vi) 305°C, benzyl benzoate.

flash vacuum pyrolysis (FVP) conditions[8] afforded the desired enone **14** as the only product, albeit in low (20%) yield. The *cis-syn-cis* stereochemical assignment of **14** follows from its mode of formation from a caged precursor and the observation that it undergoes smooth intramolecular [2+2]-cycloaddition back to **12** on exposure to sunlight. The enone transposition in **14** to **6** was readily accomplished under static thermal activation in 75% yield. The 8-step sequence from the dione **9** allowed the preparation of the key intermediate **6**, but in only about 5% overall yield, Scheme 2.

Keeping in mind the need for more material, we explored an alternative route towards the key intermediate **6**. In this approach, the symmetrical *bis*-enone **8** was to serve as the starting point which could be conveniently prepared in multi-gram quantities from the dione **9**

by FVP method.[8] Thermally induced enone transposition in **8** to **7** and regioselective reduction of the less substituted enone carbonyl using substoichiometric amounts of $NaBH_4$ in the presence of $CeCl_3$[11] afforded the *endo*-alcohol **15a** as a single diastereomer. The assignment of *endo*-stereochemistry to the allylic hydroxyl group in **15a** was mainly based on the precedence that hydride addition preferentially occurs from the *exo*-face in diquinanes. Initially, reductive deoxygenation of the hydroxyl group in **15a** was attempted employing, the Robins modification[12] of Barton methodology, through its thionocarbonate derivative. Exposure of **15b** to n-Bu_3SnH in the presence of AIBN invariably resulted in low yield (25-35%) of **6**, although the starting material **15a** could be recovered and recycled, Scheme 3.

Scheme 3



Reagents and conditions: (i) Benzyl benzoate, Δ; (ii) $CeCl_3.7H_2O$, $NaBH_4$, -15°C, (iii) p-MeC_6H_4OCSCl, py., CH_2Cl_2, 20°C; (iv) TBTH, AIBN, PhH, 90°C; (v) (a) 85% HCOOH, 80°C, (b) 10% KOH- MeOH, 30%; (vi) TMSCl, NaI, CH_3CN, 0°C; (vii) TBTH, AIBN, PhH, 80°C.

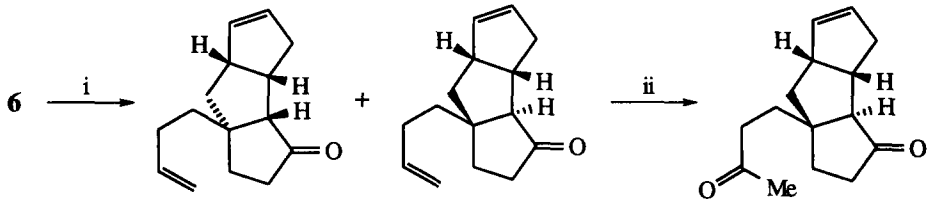
Recognizing that low yield and sluggishness of the deoxygenation reaction in **15b** could be due to the hindered *endo*-disposition of the thionocarbonate group, we sought to ameliorate this stereochemical impediment by first inverting the stereochemistry of the hydroxyl group from *endo* to *exo* in the allylic alcohol **15a**. Consequently, the *endo*-alcohol **15a** was subjected to formolysis wherein the intermediate allylic cation was regio- and stereoselectively captured by the formate anion from the *exo* -face. The resulting formate ester was gently hydrolyzed to the *exo* -allylic alcohol **16a**. Exposure of the thionocarbonate **16b** derived from the *exo* alcohol **16a** to n-Bu_3SnH-AIBN resulted in the formation of **6** in substantially improved yield (64%). Although, the stereochemical inversion device worked as anticipated and **6** was delivered in better yield, yet it was not considered good enough for our projected objective. Therefore, another route was pursued for the conversion of **15a** to **6**. The *endo*-alcohol **15a** was directly converted to the *exo*-iodide **17** in high yield by SN_2 displacement reaction employing *in situ* generated TMSI.[13] The iodide **17** was unstable to chromatographic purification and was as

such subjected to reductive deiodination[14] using n-Bu3SnH-AIBN to furnish **6** in 60% yield from **15a**, Scheme 3. This sequence was much simpler, could be scaled up easily and found satisfactory for our purpose.

Elaboration of rings 'A' and 'D'

The tricyclic enone **6** was now ready for the A-ring annulation conceptualized in Scheme 1. To this end, the required four-carbon chain was introduced *via* conjugate 1,4-addition to the enone moiety with simultaneous installation of a quaternary carbon center. Addition of Grignard reagent prepared from 4-bromo-1-butene to **6** in the presence of Cu(I) furnished a readily separable 1:2 mixture of *cis-syn-cis* and *cis-anti-cis* adducts **18** and **19** in 70% yield, in which the desired product **19** predominated, Scheme 4. The relative ring junction stereochemistry in **19** was unambiguously established through chemical correlation with a

Scheme 4



18 **19** **20**

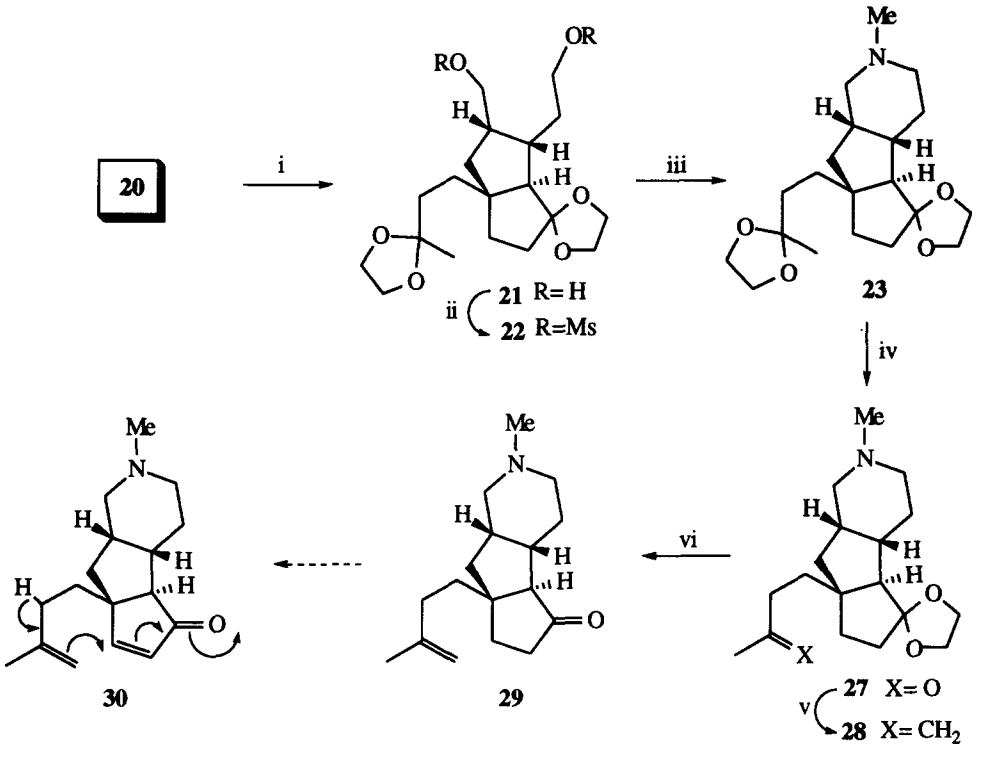
Reagents and conditions: (i) CH_2=$CHCH_2CH_2MgBr$, $Me_2S.CuBr$, THF, -78°C; (ii) $PdCl_2$, CuCl, O_2, DMF-H_2O.

compound previously prepared in our laboratory.[15] For further synthetic manipulations, the terminal olefinic moiety in the butenyl side chain of **19** was regioselectively oxidized to the methyl ketone functionality through Wacker-type oxidation, employing Tsuji's catalytic Pd(II) based methodology,[16] to furnish the enedione **20** in 85% yield.

At this stage, we preferred to first establish the elaboration of cyclopentene part structure to *N*-methylpiperidine (D-ring) and also demonstrate the methodology for the annulation of ring 'A'. Consequently, the dione **20** was transformed to the *bis*-ethylene ketal and subjected to ozonolysis with *in situ* reduction of the ozonide with excess of sodium borohydride[17] to afford the diol **21** as a single product. The diol **21** was transformed to the dimesylate **22**, which on heating in DMSO saturated with methylamine,[18] led to the facile formation of N-methylpiperidine nucleus (D-ring) **23** through sequential inter- and intramolecular displacement processes, Scheme 5.[19]

We now turned our attention towards A-ring annulation in **6** for which an intramolecular cationic enone-olefin cyclization was identified as the key step. Dione **20** on regioselective Wittig olefination furnished **24** and the carbonyl group was elaborated to the enone moiety through phenylselenation-selenoxide elimination sequence to deliver **25**, Scheme 6. Exposure of **25** to perchloric acid resulted in the contemplated cyclization to generate ring-A and afforded the tetracyclic dione **26** in high yield.

Scheme 5

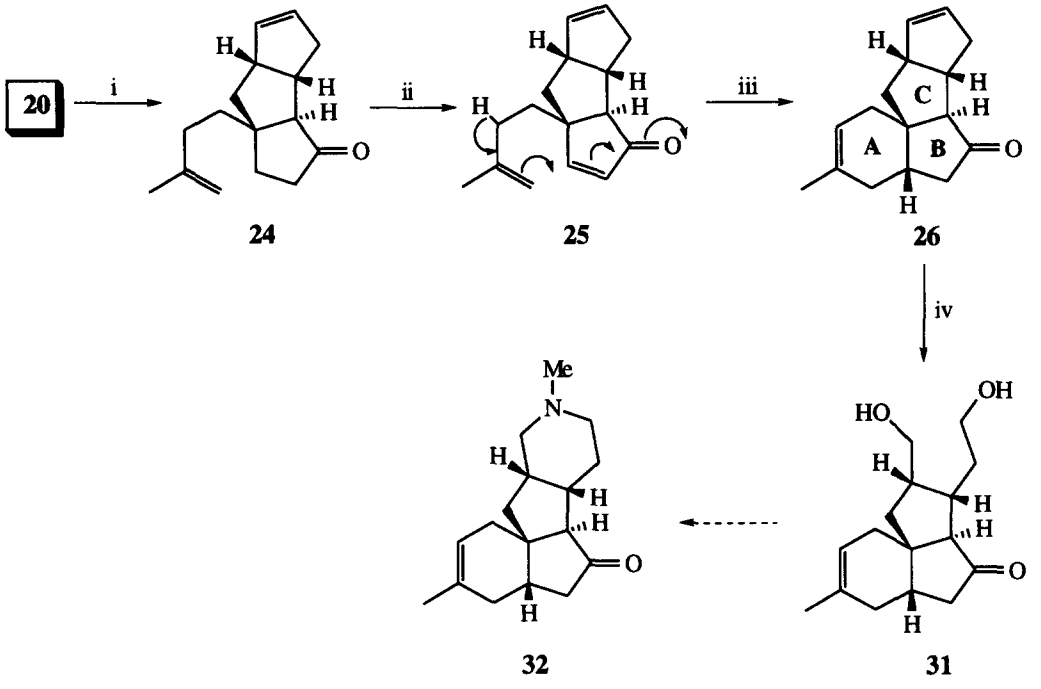


Reagents and conditions: (i) (a) $HOCH_2CH_2OH$, CSA, PhH, 90°C, (b) O_3, MeOH, -78°C, (c) $NaBH_4$, -78°C - RT; (ii) MsCl, Et_3N, CH_2Cl_2, 0°C - RT; (iii) CH_3NH_2, DMSO, 85°C, (iv) PPTS, acetone, 70°C; (v) PPh_3CH_3Br, *ter*-AmONa, PhH, RT.(vi) PPTS, moist acetone, 70°C, 24h.

The successful acquisition of advanced intermediates **23** and **26**, with correct stereochemical disposition and adequate levels of functionalization, set the stage for their further elaboration towards the target structures **1-3**. In this context, our first venture was to apply the ring-A annulation protocol to **23** to complete the tetracyclic framework of the natural products. To this end, the *bis*-ketal **23** was subjected to selective mono-deketalisation to give keto-ketal **27**. Wittig olefination of **27** with the ylide generated from methyltriphenylphosphonium bromide led to the formation of **28** in 81% yield. Hydrolysis of the ketal **28** furnished the corresponding olefinic ketone **29** in good yield in which the final carbon-carbon bond forming reaction was intended to be established through an enone-olefin cyclization, an approach successfully employed in the case of **25** (*vide supra*). Therefore, **29** was subjected to a phenylselenation-selenoxide elimination sequence,[20] Scheme 5. However, despite repeated trials **30** could not be realized, perhaps due to the susceptibility of the piperidine ring nitrogen to oxidizing agents. An alternate method for the ketone to enone transformation was explored and **29** was transformed to the trimethyl silyl enol ether and subjected to Pd(II) mediated oxidative desilylation according to Saegusa procedure,[21] but again without success. Thus, our efforts to append ring-A to **23** to attain the desired tetracyclic framework remained unsuccessful. We, therefore attempted to elaborate ring-D in **26**, having ring-A already in place. This required regioselective oxidative cleavage of the less substituted cyclopentene double bond in **26** for which precedence exists. However, all our efforts to realize the diol **31**, through

reductive ozonolysis, by employing a variety of conditions were unsuccessful. Thus, the objective of transforming **26** to the required **32** had to be abandoned, Scheme 6.

Scheme 6

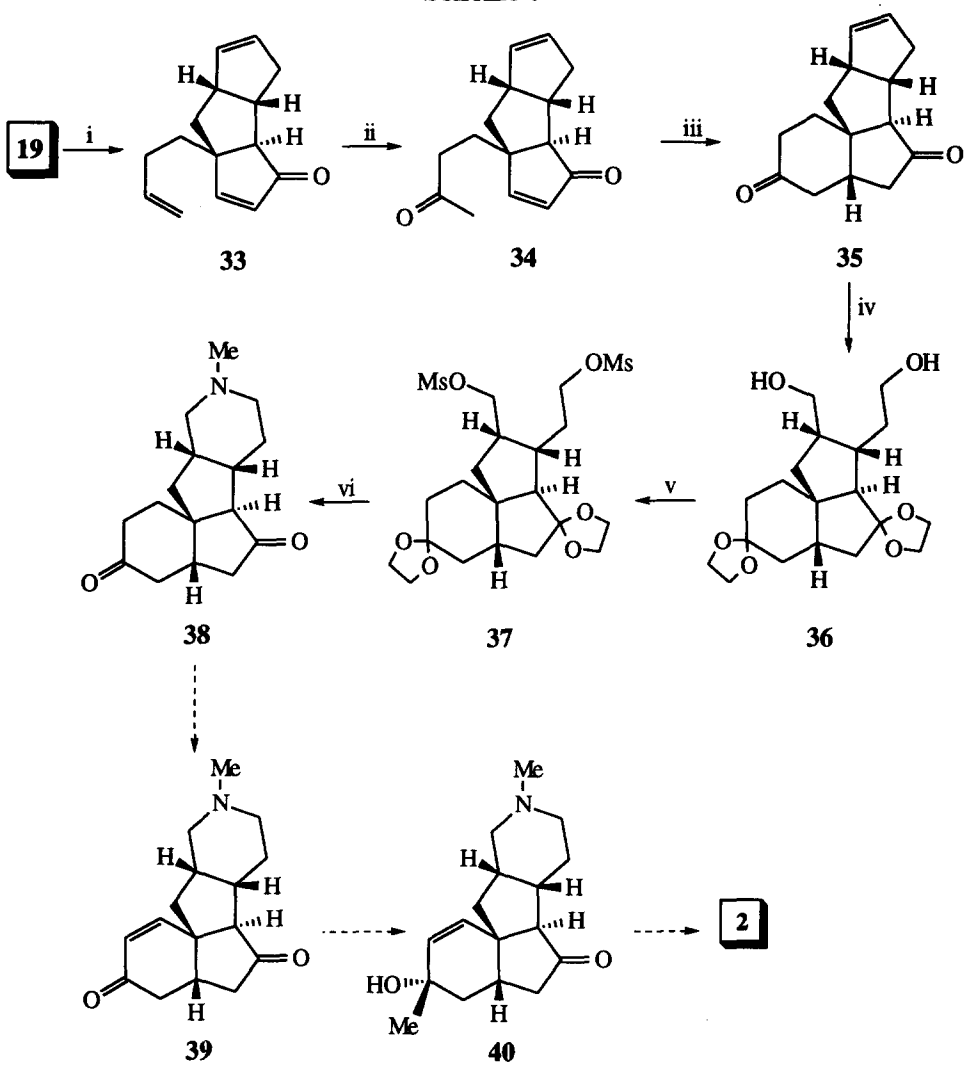


Reagents and conditions: (i) PPh_3CH_3Br, t-AmONa, PhH, RT.;(ii) (a)LHMDS, PhSeCl, THF, - 78°C- RT ;(b) 30% H_2O_2, py, DCM, 0- 20°C, 1h; (iii) 70% $HClO_4$, EtOAc, 80°C, 0.5h; (iv) (a) O_3, MeOH, -78°C, (b) $NaBH_4$, -78°C - RT.

Synthesis of deoxymagellaninone 32

Having been thwarted in the attempts to access the desired tetracyclic framework, we returned to compound **19** and chose to incorporate the A-ring early in the synthesis and at a different oxidation level (*cf.* **26**) to avoid the problems associated with enone generation or piperidine ring formation. For this purpose, a different strategy based on intramolecular Michael addition was envisaged. Implementation of the phenylselenation- selenoxide elimination sequence in **19** readily delivered the enone **33** in 81% yield (Scheme 7).[20] Trienone **33** was regioselectively oxidized to the diene dione **34** *via* Tsuji reaction[16] as described previously (see **19**→**20**, Scheme 4), in 80% yield. Deprotonation of **34** with sodium hydride in THF resulted in the contemplated cyclization through an intramolecular Michael addition to afford the desired tetracyclic dione **35** in 78% yield. The assigned stereochemistry at the newly generated ring junction stereocenter in **35** was mainly based on the well-precedented expectation that the bicyclo[3.3.0]octanes predominantly react on the convex surface.

Scheme 7



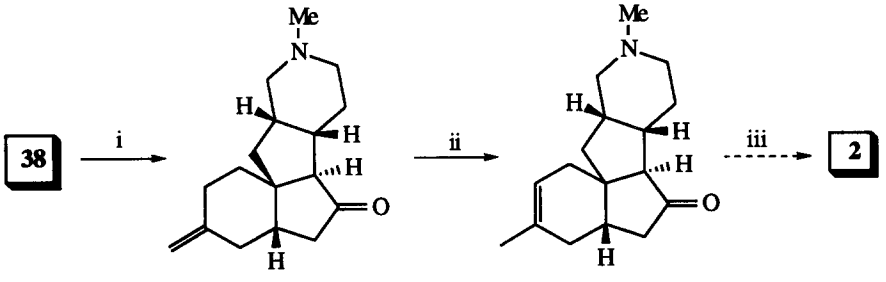
Reagents and conditions: (i) (a) LHMDS, PhSeCl, THF-HMPA, -78 - 0°C, (b) 30% aq.H_2O_2, Py., CH_2Cl_2, 0 - 20°C; (ii) $PdCl_2$, CuCl, O_2, DMF-H_2O; (iii) NaH, THF, 50°C; (iv) (a) $HOCH_2CH_2OH$, CSA, PhH, 90°C, (b) O_3, MeOH, -78°C, (c) $NaBH_4$, -78°C - RT, (v), MsCl, Et_3N, CH_2Cl_2, 0°C - RT; (vi) (a) CH_3NH_2, DMSO, 85°C (b) PPTS, acetone, 70°C.

With the A-ring successfully installed, with correct stereochemistry at all the five stereogenic centers, the stage was once again set for the elaboration of the cyclopentene part-structure in **35** to *N*-methylpiperidine (D-ring). Consequently, tetracyclic dione **35** was transformed into the *bis*-ketal **36** under standard conditions and the sequence of reactions previously described for **20** in Scheme 5 was repeated. Thus, ozonolysis, $NaBH_4$ reduction and mesylation afforded the dimesylate **37** in 75% yield. Methylamine mediated cyclization in **37** led to the formation of **38**, representing the complete tetracyclic framework of our target molecules, with fully secured stereochemistry at all the stereogenic centers, in 65% yield.

The next and final stage in the synthesis of **1-3** required a 1,3-carbonyl transposition[22] and introduction of the methyl group in the A-ring of **38**. As illustrated in Scheme 7, a sequence involving enone generation (**38**→**39**) and 1,3-alkylative carbonyl transposition[23] *via* **40** was expected to directly deliver magellanione **2**. However, all our efforts to transform **38** to the corresponding enone were unsuccessful. A variety of bases under different reaction conditions were employed to implement the phenylselenation-selenoxide elimination sequence and also the Saegusa procedure[21] involving silyl enol ether formation and Pd(II) catalyzed oxidative desilylation but without any success. These reactions work for dienone **19** but not for **38** and the ketone **29**, suggesting an apparent incompatibility of this reaction in the presence of *N*-methylpiperidine ring.

Therefore, as an alternative we investigated the possibility of introducing the requisite olefinic methyl group through a Wittig olefination in **38** followed by isomerization, as depicted in Scheme 8. Reaction of **38** with methyltriphenylphosphorane under controlled conditions led to the formation of the desired olefinic ketone **41** in 78% yield. Acid mediated isomerization of the exocyclic double bond in **41** in the presence of PTSA in refluxing benzene resulted in the formation of deoxymagellaninone **32** as the only isolable product in 81% yield. It was expected that the regioselective allylic oxidation of the cyclohexene moiety in **32** would directly deliver magellaninone **2**. However, all attempts to transform **41** to **2** through various allylic oxidation procedures resulted in the formation of uncharacterisable products, once again underscoring the vulnerability of the *N*-methylpiperidine moiety present to oxidative manoeuvres.

Scheme 8



41 32

Reagents and conditions: (i) Ph_3PCH_3Br, t-AmONa, PhH, RT; (ii) PTSA, PhH, 90°C; (iii) PDC, t-BuOOH, PhH or SeO_2, t-BuOOH etc.

In summary, we have achieved the synthesis of deoxymagallinone **32** representing the complete framework present in the lycopodium alkaloids of magellaninone and paniculatine-type through a short and regioselective approach from readily available starting materials. While the final step in the synthesis of natural products **1-3**, involving routine functional group transformations on **32** and **39** has eluded us, a flexible and reliable methodology for the construction of the tetracyclic ring system present in the natural products has been established.

Experimental

General: Mps were determined on a Buchi SMP-20 apparatus and are uncorrected. IR absorption spectra were run on a Perkin-Elmer model 297 or 1310 spectrophotometers. ^1H (100

MHz) and ^{13}C (25 MHz) NMR spectra were recorded on a Jeol FX-100 spectrometer (unless otherwise noted) using $CDCl_3$ as solvent and Me_4Si as internal standard. Chemical shift values are given in δ (ppm) units and *J* values are in Hz. Microanalyses were performed with a Perkin-Elmer 240C elemental analyzer. All moisture sensitive reactions were carried out using standard syringe-septum techniques under nitrogen atmosphere. Dichloromethane was distilled over P_2O_5. Tetrahydrofuran (THF), diethyl ether and dimethoxy ethane were distilled from Na-benzophenone ketyl prior to use. All solvent extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated on a Buchi EL rotary evaporator. Yields reported are isolated yields of material judged homogenous by tlc and NMR spectroscopy.

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undeca-8,11-dione 9was prepared as reported,[9] mp 243-44°C.

***exo*-11-Bromopentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one 11** was prepared following the procedure described by Eaton *et al.*[10a] by treating the crude *endo*-hydroxy ethylene ketal **10** with 48% aq.HBr at 80°C for 3h. Cooling in an ice-bath and filtration led to **11** as a white crystalline solid; mp 84-85°C [Lit. mp 84.5-85.3°C][10a] in 90% yield.

Pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one 12 *Method A*: Bromoketone **11** (840mg, 3.5mmol) in dry ether (8ml) was slowly added (5min) to a stirred solution of Li-NH_3 prepared from freshly cut Li metal (400mg) and liq.NH_3 (70ml) maintained at -78°C. After 20 min. solid NH_4Cl was added and the ammonia was allowed to evaporate. The residue was diluted with saturated aq.NH_4Cl solution (25ml) and extracted with diethyl ether (3 x 30ml). Usual work-up furnished a mixture of epimeric alcohol (558mg, 98%). To this crude mixture of alcohols (538mg, 3.32mmol) in dry CH_2Cl_2 (20ml), was added pyridinium chlorochromate (1.43g, 6.63mmol) and 4Å molecular sieves (3.5g). The reaction mixture was stirred at room temperature for 3 h and diluted with dry ether (10ml) and filtered through a florisil pad. The filtrate was concentrated and the residue obtained was charged on a 15% $AgNO_3$-silica gel column. Elution of the column with 8% EtOAc-hexane gave **12** (71mg, 13%) as colorless crystals; mp 193-195°C; IR (KBr): 1745 cm^{-1}; ^1H NMR: δ 2.96-1.92 (8H, m), 1.84-1.20 (4H, m); ^{13}C NMR: δ 220.9, 52.7, 48.3, 48.0, 44.1, 43.3, 43.0, 39.2, 37.3, 36.4, 30.8. Further elution with the same solvent afforded **13** (41mg, 8%); mp 191-192°C [Lit.[10a] mp 192-93°C], which had identical IR and ^1H NMR spectral data to that reported in the literature.

Method B: A mixture of **11** (1.0g, 4.18mmol), ethyleneglycol (0.29ml, 5.2mmol) and PTSA (20mg, 0.10mmol) was heated at reflux in benzene (50ml) for 4h using a Dean-Stark water separator. The reaction mixture was cooled and neutralized with aq.$NaHCO_3$ solution. The benzene layer was separated and concentrated to furnish *exo*-11-bromopentacyclo-[5.4.0^{2,6}.0^{3,10}.0^{5,9}]undecan-8-one ethylene ketal as an oily liquid (1.12g, 95%); IR (neat): 2950, 1330, 1110 cm^{-1}; ^1H NMR: δ 5.16 (1 H, brs), 4.02-3.68 (4 H, m), 3.16-1.96 (8 H, series of m), 1.84-1.28 (2 H, ABq); Anal. Calcd. for $C_{13}H_{15}O_2Br$: C, 55.14; H, 5.34. Found: C, 55.20; H, 5.28. The bromo ketal (740mg, 2.61mmol) was reduced with Li-NH_3 as described previously and the ketal thus obtained was hydrolyzed with 20% HCl in THF to afford **12** (250mg, 37% from **11**), which was identical in all respects with the product obtained in the earlier experiment.

Tricyclo[6.3.0.0^{2,6}]undecan-4,9-diene-3-one 14. The pentacyclic monoketone **12** (500mg, 3.12mmol) was subjected to flash vacuum pyrolysis (640 ± 10°C, 0.3 mm)[8] using a quartz tube

(1.5 x 30 cm) and the pyrolysate was directly charged onto a silica gel column. Elution with 8% EtOAc-hexane initially furnished the starting mono ketone **12** (100mg, 20%) followed by the tricyclic enone-olefin **14** (80mg, 16%) as a pale yellow oil; IR (neat): 3050, 2950,1700, 1595 cm^{-1}; ^1H NMR: δ 7.42 (1 H, dd, *J* 7.0, 3.0), 5.84 (1 H, dd, *J* 7.0, 3.0), 5.56-5.32 (2 H, m), 3.54-1.36 (8 H, m); ^{13}C NMR: δ 212.2, 167.2, 136.1, 133.4, 130.8, 54.2, 52.6, 50.1, 46.1, 33.7, 33.3. Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.54. Found: C, 82.60; H, 7.57.

Tricyclo[6.3.0.0^{2,6}]undeca-2(6),9-diene-3-one 6. A solution of the olefinic enone **14** (160mg, 1.0mmol) in benzyl benzoate (3.0ml) was heated at 305 ± 5°C for 3 min. The dark solution was charged onto a silica gel column after cooling to room temperature. Elution with 8% EtOAc in hexane gave the enone **6** (120mg, 75%); IR (neat): 3030, 1695, 1630 cm^{-1}; ^1H NMR: δ 5.70-5.41 (2 H, m), 3.98-2.0 (10 H, series of m); ^{13}C NMR: δ 204.2, 184.7, 150.2, 133.2, 129.1, 54.1, 40.8, 40.2, 37.1, 35.3, 25.3. Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.54. Found: C, 82.50; H, 7.58.

***endo*-3-Hydroxytricyclo[6.3.0.0^{2,6}]undeca-1(8),4-dien-11-one 15a**: The *bis*enone **7**[8] (2.47g, 14.2 mmol) was dissolved in a solution of $CeCl_3.7H_2O$ (5.3g, 14.2mmol) in dry methanol (35ml) and was cooled to -15°C. To this stirred solution sodium borohydride (275mg, 7.27mmol) was added in small portions over a period of 20min. under N_2. The reaction mixture was stirred for another 20min at the same temperature and methanol was removed under reduced pressure. The residue was diluted with water (20ml) and extracted with ethyl acetate (4 x 60ml). The material obtained after usual work-up was charged on a silica gel (50g) column. Elution with 60% ethyl acetate-hexane furnished the *endo*-allylic alcohol **15a** (2g, 80%), which was crystallized from DCM-hexane; mp: 57-58°C; IR(KBr): 3350, 3030, 1670, 1615, 1380, 1060 cm^{-1}; ^1H NMR: δ 5.8-5.46 (2H, m, -HC=CH-), 4.98 (1H, d, J=7Hz, -CH-OH), 3.88-2.06 (9H, series of m); ^{13}C NMR: δ 206.4,187.1, 147.4, 135.4,132.4,77.3, 53.6, 47.7, 40.3, 37.3, 25.9; Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H,6.86. Found: C, 74.88; H,6.89.

***endo*-3-O-(p)Tolylthionocarbonatotricyclo[6.3.0.0^{2,6}]undeca-1(8),4-dien-11-one 15b**: To a solution of endo-allylic alcohol **15a** (488mg, 2.77mmol) in dry DCM was added pyridine (0.56ml, 7mmol) under N_2. To this stirred solution at 0°C was added O-(*p*)-tolylchloro thionoformate (0.4ml, 3.32mmol) and the reaction was allowed to warm to room temperature. After 3h, the reaction mixture was quenched with water (10ml) and extracted with DCM (3 x 20 ml). The residue obtained after the usual work-up was filtered through a silica gel column to furnish the thionocarbonate **15b** (780mg, 86% yield); IR(neat): 3030, 1720, 1690, 1640, 1505, 1200, 1110 cm^{-1}; ^1H NMR: δ 7.24-6.94 (4H, ABq), 6.12-5.94 (1H, m, -HC=CH-), 5.72-5.56 (1H, m), 3.8-3.58 (1H, m), 2.84-2.38 (8H, m), 2.3 (3H, Ar-CH_3). Anal. Calcd. for $C_{19}H_{18}O_3S$: C, 69.92; H, 5.56. Found: C, 70.06; H,5.60.

Reduction of 15b with tributyltinhydride to 6: To a stirred solution of thionocarbonate **15b** (82mg, 0.25mmol) in dry benzene (20ml) was added tributyltinhydride (0.20ml, 0.75mmol) and catalytic amount of AIBN under N_2. The reaction mixture was refluxed for 34h. Benzene was removed under reduced pressure and the residue was chromatographed on a silica gel (5g) column. Elution of the column with 3% ethyl acetate-hexane eliminated the tin derived impurities. Continued elution of the column with 15% ethyl acetate-hexane furnished the enone-olefin **6** (16mg, 40%), which was identical in all respects with the product obtained above.

***exo*-3-Hydroxytricyclo[6.3.0.0^{2,6}]undeca-1-(8),4-dien-11-one 16a** A stirred solution of allylic alcohol **15a** (1.4g, 7.95mmol) in 98-100% formic acid (15ml) was heated at 80°C for 45min. The dark residue obtained after the removal of formic acid under reduced pressure was treated with 10% methanolic KOH solution (10ml). After stirring for 1h, methanol was removed under vacuum and the residue was diluted with water (15ml) and extracted with ethyl acetate (4 x 25ml). The crude mixture obtained after the usual work-up was charged on a silica gel (30g) column. Elution with 50% ethyl acetate-hexane first furnished the *endo*-alcohol **15a** (200mg). Further elution of the column with the same solvent gave the *exo*-alcohol **16a** (900mg, 78% yield based on recovery of **15a**); mp: 80-81°C; IR(KBr): 3400, 3050, 1670(br), 1625, 1035, 1015, 750 cm^{-1}; ^{1}H NMR : δ 6.04-5.34 (2H, m, -CH=CH-), 4.68 (1H, br s, -CH-OH) 4.34-1.96 (9H, series of m); ^{13}C NMR: δ 204.7, 185.6, 147.9, 138.2, 131.5, 77.8, 52.9, 51.7, 40.9, 36.1, 25.6. Anal. Calcd. for $C_{11}H_{12}O_2$: C, 74.97; H,6.82. Found: C, 74.61; H,6.78.

***exo*-3-O-(*p*)-Tolylthionocarbonatotricyclo[6.3.0.0^{2,6}]undeca-1(8),4-dien-11-one 16b**:The *exo*-thionocarbonate was made in 87% yield from exo-allylic alcohol **16a** following the conditions used for making **15b** and described in an earlier experiment; IR(neat): 1720, 1690, 1635, 1505, 1195, 1170, 1110 cm^{-1}; ^{1}H NMR: δ 7.24-6.96 (4H, ABq), 6.16-5.96 (1H, m), 5.76-5.56 (1H, m), 4.54-2.36 (9H, series of m), 2.34 (3H, s, Ar-CH_3); Anal. Calcd. for $C_{19}H_{18}O_3S$: C, 69.92; H,5.56. Found: C, 69.42; H,5.49.

Reduction of 16b with tributyltinhydride to 6: The *exo*-thionocarbonate **16b** (5.5g, 16.85mmol) was dissolved in dry benzene (600ml) and tributyltinhydride (12ml, 38.1mmol) and AIBN (60mg) were added under N_2 with stirring. The reaction mixture was refluxed for 4h, cooled and washed with 2% ammonia solution (to remove tin impurities) and dried. The residue was purified on a silica gel (70g) column. Elution of the column with 15% ethyl acetate-hexane furnished the enone-olefin **6** (1.42g, 84% based on recovered **16b**), which was identical in all respects with the product obtained above. Further elution of the column with 50% ethyl acetate-hexane furnished the unreacted thionocarbonate **16b** (2.062g) which was recycled.

***exo*-3-Iodotricyclo[6.3.0.0^{2,6}]undecan-1(8),4-dien-11-one 17**: Trimethylchlorosilane (1.87g, 17.2 mmol) was added dropwise (5 min) to a stirred and cooled (0°C) suspension of oven dried (150°C) sodium iodide (2.58g, 17.2mmol) in acetonitrile (30ml), under N_2.[13] A solution of **15a** (3.0g, 17.04mmol) in acetonitrile (8ml) was then added dropwise at the same temperature and the reaction mixture was allowed to warm-up and then diluted with water (60ml) and extracted with ether (3 x 30ml). The combined ether extracts were washed with 10% sodium thiosulfate (30ml) and worked up in usual fashion to yield the crude iodide **17** (4.48g, 92%) as a viscous liquid; IR (Neat):2920, 1690, 1625, 765 cm^{-1}; ^{1}H NMR: δ 6.04-5.88 (2 H, m), 5.16 (1 H, brs), 4.14-3.76 (2 H, m), 2.86-2.30 (6 H, m).

Reductive deiodination of 17 to 6. Reduction of **17** (4.3g, 15.0mmol) with n-tributyltin-hydride (4.5g, 15.4mmol) in the presence of catalytic amounts of AIBN in benzene (1.5 lit) at 80°C was carried out as described for **15b** to give **6** (1.56g, 65%). This product was identical by comparison (IR, ^{1}H NMR) with the sample prepared from **15b**.

6-(But-3-enyl)tricyclo[6.3.0.0^{2,6}]undec-9-en-3-one 19: Into a 3-necked RB flask was introduced freshly crystallized cuprous bromide-dimethylsulfide complex (230mg, 1.12mmol), dimethylsulfide (3ml) and dry THF (3ml) under N_2. To this stirred solution at -78°C was added

the 1-butenylmagnesium bromide solution (4.5mmol). After 1h, the enone **6** (160mg, 1mmol) in dry THF (4ml) was added to the cuprate reagent in a dropwise manner. After stirring for another 1h at -78°C, the reaction was quenched by adding brine (10ml). The reaction mixture was extracted with ether (3 x 20 ml) and washed with basic NH_4Cl solution and dried. The oily residue obtained after the removal of solvent was charged on a silica gel (10g) column. Careful elution with 2% ethyl acetate-hexane furnished the *cis,syn,cis*-compound **18** (50mg); IR(neat): 3050, 1735, 900 cm^{-1}; ^1H NMR: δ 6.02-5.4 (3H, m, -CH=CH- and CH2=CH-), 5.24- 4.8 (2H, m), 3.52-1.02 (15H, series of m). ^{13}C NMR: δ 222.2, 138.9, 135.2, 130.1, 114.5, 61.2, 53.9, 52.3, 46.2, 42.0, 40.1, 38.3, 33.3, 30.9, 29.4. Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H, 9.32. Found: C, 83.18; H,9.36. Further elution of the column with the same solvent furnished the required *cis,anti,cis*-compound **19** (100mg, combined yield of **18** and **19** was 70%); IR(neat) : 3050, 1735, 900 cm^{-1}; ^1H NMR : δ 6.0-5.44 (3H, m, -CH=CH- and CH_2=CH-), 5.12-4.8 (2H, m, CH_2=CH-), 3.42-1.2 (15H, series of m). ^{13}C NMR: δ 222.2, 138.9, 135.4, 128.7, 114.5, 67.6, 53.4, 51.6, 45.3, 41.3, 40.3, 38.3, 36.2, 30.6, 29.6. Anal. Calcd. for $C_{15}H_{20}O$: C, 83.28; H,9.32; Found: C, 83.14; H,9.34.

6-(3-Oxobutyl)tricyclo[6.3.0.0^{2,6}]undec-9-en-3-one 20: In an RB flask was placed $PdCl_2$ (60mg, 0.34 mmol), CuCl (500mg, 5mmol), dimethylformamide (8ml) and water (3ml) under O_2 atmosphere and the contents were stirred for 1h. To this activated mixture, **19** (300mg, 1.39mmol) was added in dimethyl formamide (5ml) and stirring was continued for 3h at room temperature. The reaction mixture was quenched with 10% HCl (5ml) and extracted with ether (3 x 20 ml). The residue obtained after usual work-up was charged on a silica gel (10g) column. Elution of the column with 20% ethyl acetate-hexane furnished the diketone **20** (274mg, 85% yield); IR(neat): 3030, 1720 (br) cm^{-1}; ^1H NMR : δ 5.7-5.4 (2H, m, -CH=CH-), 3.4-1.4 (15H series of m), 2.12 (3H, s, -C-CH_3); ^{13}C NMR: δ 221.6, 208.6, 135.1, 128.9, 67.4, 52.7, 51.5, 45.1, 40.7, 40.2, 39.6, 36.0, 32.2, 30.4, 29.9. Anal. Calcd. for $C_{15}H_{20}O_2$. C, 77.54; H, 8.67. Found: C, 77.60; H,8.70.

6-(3-Methyl-but-3-enyl)Tricyclo[6.3.0.0^{2,6}]undec-9-en-3-one 24: To a stirred suspension of methyltriphenylphosphonium bromide (160mg, 0.45mmol) in dry benzene (8ml) was introduced sodium t-amyloxide (33mg, 0.3mmol) in dry benzene (2ml) under N_2. After 20min the diketone **20** (60mg, 0.26mmol) in benzene (6ml) was introduced and stirring was continued for another 10min. The reaction mixture was quenched with water and extracted with ether (3 x 10 ml). The residue obtained after work-up was charged on a silica gel (5g) column. Elution with 5% ethylacetate-hexane furnished the monomethylenated ketone **24** (45mg, 75% yield); IR(neat): 3030, 1730, 890 cm^{-1}; ^1H NMR: δ 5.76-5.44 (2H, m, -CH=CH-), 4.76-4.68 (2H, m, -C=CH_2), 3.42-1.3 (15H, series of m), 1.74 (3H, br, s, H_2C=C-CH_3) Anal. Calcd. for $C_{16}H_{22}O$: C, 83.43; H, 9.62. Found: C, 83.68; H,9.58.

6-(3-Methyl-but-3-enyl)tricyclo[6.3.0.0^{2,6}]undec-9,4-dien-3-one 25: Lithium hexamethyldisilzide was generated by introducing hexamethyldisilazane (0.13ml, 0.6mmol) at-78°C to n-butyllithium (0.4ml, 0.48mmol, 1.2M solution in hexane) under N_2. Keto-diolefin **24** (100mg, 0.43mmol) in THF (4ml) was introduced and after 30min. the enolate was quenched with phenylselenenyl chloride (95mg, 0.5mmol) in THF (5ml). The reaction was allowed to warm to room temperature and the usual work-up furnished the crude phenylseleno-ketones. These were dissolved in DCM (10ml) and pyridine (0.08ml, 1mmol) was added. The solution was cooled to 0°C and 30% aq.H_2O_2 (15 drops) was added. After 30min, at room temperature, the reaction mixture was diluted and extracted with DCM (3 x 10 ml). The residue obtained after

the removal of solvent was charged on a silica gel (5g) column. Elution with 5% ethyl acetate-hexane furnished the enone **25** (58mg, 58% yield); IR(neat): 3050, 1700, 1640, 1590, 890 cm^{-1}; ^1H NMR : δ 7.42 (1H, d, J=6Hz, -HC=CH-C=O), 5.96 (1H, J=6Hz, -HC=CH-C=O), 5.78-5.44 (2H, m, -CH=CH-), 4.64 (2H, br s), 3.2-1.4 (11H, series of m), 1.68 (3H, br s). ^{13}C NMR: δ 212.6, 170.4, 145.3, 135.1,130.9, 129.4, 110.0, 62.5, 60.1, 51.2, 47.0, 41.3, 39.9, 37.2, 33.7, 22.4. Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.29; H,8.79.

Perchloric acid mediated cyclization of 25: 4-Methyltetracyclo[7.6.0.0^{1,6}.0^{10,14}]-pentadeca-3,12-dien-8-one 26: To a stirred solution of enone-diolefin **25** (45mg, 0.2mmol) in ethyl acetate (10ml) was added 70% perchloric acid (3 drops) and the contents were refluxed for 30min. The reaction mixture was diluted with water and extracted with ethyl acetate (2 x 10 ml). The residue obtained after the usual work-up was filtered through a small silica gel column to give the tetracyclic keto-olefin **26** (40mg, 89% yield); IR (neat): 3030, 1730 cm^{-1}; ^1H NMR: δ 5.66-5.4 (2H, m, -CH=CH), 5.32-5.16 (1H, m, -C=CH-), 3.36-1.3 (14H series of m), 1.62 (3H, br s, -CH=C-CH_3); ^{13}C NMR: δ 221.7,135.5, 134.5, 128.4, 123.6, 65.5, 51.2 (2C), 45.3, 43.9, 42.4, 40.3, 39.3, 30.5, 27.8, 23.5. Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H,8.83. Found: C, 84.10; H,8.80.

5-(3-Ethylenedioxybutyl)-7-mesyloxymethyl-8-(2-mesyloxyethyl)bicyclo[3.3.0]octan-2-one ethylene ketal 22: In a RB flask fitted with Dean-Stark water separator was placed the diketone **20** (295mg, 1.27mmol), ethanediol (205mg, 3.3.mmol), camphorsulfonic acid (5mg) and benzene (30ml). The contents were refluxed for 3h. The flask was cooled and the contents were poured into sat.$NaHCO_3$ solution (10ml). Extraction with ethyl acetate (3 x 20 ml) furnished the *bis*-ketal (370mg) which was used as such for the next step. Into a solution of the *bis*-ketal in methanol (40ml), ozone was bubbled until blue color appeared at -78°C. Excess ozone was flushed-out with a slow stream of N_2 for two min. and sodium borohydride (215mg, 5.7mmol) was added in small portions over a period of 20min and the reaction mixture was allowed to warm to room temperature. Acetone (1ml) was added to the reaction mixture and methanol was removed under reduced pressure. The residue was diluted with water (15ml) and thoroughly extracted with chloroform (5 x 25 ml) to furnish the *bis*-ketal diol **21**.

The crude diol **21** obtained above was dissolved in dry DCM (20ml) and triethylamine (0.6ml, 4.3mmol) was added. The contents were cooled to -23°C and methanesulfonyl chloride (0.26ml, 3.2mmol) was added under N_2. The reaction mixture was allowed to warm to room temperature and the reaction was quenched by adding sat.$NaHCO_3$ solution (10ml). Extraction with DCM (3 x 25 ml) and work-up furnished a residue which was charged on a silica gel (15g) column. Elution with 50% ethyl acetate-hexane gave the *bis*-ketal dimesylate **22** (455mg, 70% from **20**) as a syrupy liquid; IR (neat): 1340, 1160, 950 cm^{-1}; ^1H NMR : δ 4.36-4.08 (4H, m, (-CH_2-OMs)$_2$), 3.92 (4H, s), 3.90 (4H, s), 3.03 (3H, s), 3.02 (3H, s), 2.72-1.24 (15H, series of m), 1.3 (3H, s,-C-CH_3); ^{13}C NMR: δ 117.6, 109.6, 69.9, 68.6, 64.6, 64.3(2C), 63.9, 61.1, 50.3, 46.1, 41.0, 40.1, 38.8, 37.0(2C), 36.6, 34.9, 34.3, 28.0, 23.5. Anal. Calcd. for $C_{21}H_{36}O_{10}S_2$: C, 49.21; H,7.08. Found: C, 49.34; H,7.12.

8-(3-Ethylenedioxybutyl)-10-methyl-10-azatricyclo[6.4.0.0^{2,6}]dodecan-3-one ethylene ketal 23: A solution of the dimesylate **22** (270mg, 0.53mmol) in dry DMSO (10ml) saturated with dry methylamine gas at ~15C and was placed in a sealed tube. The sealed tube was kept in an oil bath at 85-90°C for 16h. The seal tube was cooled, carefully opened and the reaction mixture was poured into water (20ml). The aqueous phase was extracted with DCM (3 x 20 ml),

washed and dried. The residue was filtered through a short basic alumina column to furnish the tricyclic *bis*-ketal **23** (145mg, 78% yield); IR(neat): 2950, 2770, 1450, 1370 cm^{-1}; ^1H NMR: δ 4.0-3.8 (8H, m), 2.84-1.24 (19H series of m), 2.24 (3H, s, -N-CH_3), 1.34 (3H, s, -C-CH_3); ^{13}C NMR: δ 118.3, 110.0, 64.5, 64.3 (2C), 63.6, 62.3, 57.0, 55.3, 50.9(2C), 44.8, 41.2, 38.6, 37.7, 37.3, 35.1(2C), 28.9, 23.6. Anal. Calcd. for $C_{20}H_{33}NO_4$: C, 68.34; H,9.46; N, 3.98. Found: C, 68.18; H,9.49; N, 3.70.

6-(3-Oxobutyl)-10-methyl-10-azatricyclo[6.4.0.0^{2,6}]dodecan-3-one ethylene ketal 27: To a stirred solution of tricyclic *bis*-ketal **23** (120mg, 0.34mmol) in dry acetone was added pyridinium-p-toluenesulfonate (PPTS) (130mg, 0.52mmol) and the contents were refluxed for 4h. Acetone was removed and the residue was diluted with sat.$NaHCO_3$ solution. Extraction with DCM (3 x 15 ml) and filtration through a small alumina column yielded the keto-ketal **27** (79mg, 75%) as an oily liquid. IR(neat): 2950, 2760, 1710 cm^{-1}; ^1H NMR : δ 3.88 (4H, s, -O-CH_2-CH_2-O-), 2.74-1.24 (19H, series of m), 2.20 (3H, s, -N-CH_3), 2.12 (3H, -C-CH_3); ^{13}C NMR: δ 209.4, 118.3, 64.7, 63.8, 62.5, 57.0, 55.2, 50.7, 46.8, 41.3, 38.8, 37.9, 36.9, 35.1(2C), 29.8, 28.8. Anal. Calcd. for $C_{18}H_{29}NO_3$: C, 70.33; H,9.48; N, 4.55. Found: C, 70.10; H, 9.53; N, 4.53.

8-(3-Methylbut-3-enyl)-10-methyl-10-azatricyclo[6.4.0.0^{2,6}] dodecan-3-one ethylene ketal 28: To a stirred suspension of methyltriphenylphosphonium bromide (215mg, 0.6mmol) in dry benzene (10ml) was added a solution of sodium t-amyloxide (33mg, 0.3mmol) in benzene (1ml) under N_2. After 25min. the keto-ketal **27** (60mg, 0.196mmol) in dry benzene was added to the ylide solution. The reaction mixture was stirred at room temperature for another 10min. and quenched with water (5ml) and extracted with ethyl acetate (3 x 10ml). The residue obtained after the usual work-up was charged on a basic alumina (5g) column. Elution with 50% ethyl acetate-hexane furnished the ketal **28** (51mg, 85.5%); IR (neat): 3050, 2900, 2760, 885 cm^{-1}; ^1H NMR: δ 4.6 (2H, br s, -C=CH_2), 3.84 (4H, s, -O-CH_2- CH_2-O), 2.68-1.24 (19H, series of m), 2.16 (3H, s, N-CH_3), 1.66 (3H, br s, -H_2C=C-CH_3). ^{13}C NMR: δ 146.6, 118.5, 109.8, 64.7, 63.8, 62.7, 57.2, 55.6, 51.3, 46.9, 41.9, 41.3, 38.8, 37.9, 35.3, 35.2, 33.8, 29.1, 22.8; Anal. Calcd. for $C_{19}H_{31}NO_2$: C, 74.71; H,10.22; N, 4.58. Found: C, 73.96; H,10.25; N, 4.61.

8-(3-Methyl-but-3-enyl)-10-methyl-10-azatricyclo[6.4.0.0^{2,6}]dodecan-3-one 29: To a stirred solution of ketal **28** (25mg, 0.08mmol) in moist acetone (8ml) was added PPTS (41mg) and the mixture was refluxed for 24h. Acetone was removed and the residue was diluted with sat.$NaHCO_3$ solution. Extraction with DCM (3 x 5 ml), washing and drying furnished a residue which was filtered through a basic alumina column to furnish the ketone **29** (18mg, 85% yield) as an oily liquid; IR(neat): 3050, 2760, 1730, 1640, 885 cm^{-1}; ^1H NMR: δ 4.68 (2H, br s, -C=CH_2), 2.74-1.24 (19H, series of m), 2.2 (3H, s, -N-CH_3), 1.74 (3H, br s, -H_2C=C-CH_3); ^{13}C NMR: δ 221.8, 145.9, 109.7, 63.5, 56.9, 54.9, 50.0, 46.8, 41.7, 40.7, 40.4, 38.6 (2C), 33.7, 32.5, 28.3, 22.7. Anal. Calcd. for $C_{17}H_{27}NO$: C, 78.11; H, 10.33; N, 5.35. Found: C, 78.00; H, 10.39; N, 5.36.

6-(But-3-enyl)tricyclo[6.3.0.0^{2,6}]undeca-4-9-dien-3-one 33: To the lithium hexamethyldisilazide base [prepared by dropwise addition of hexamethyldisilazane (0.3ml, 1.4mmol) to n-butyl lithium, 1.2M solution in hexane (1ml, 1.2mmol) at -78°C]. was added the ketone **19** (216mg, 1mmol) in dry THF (4ml). The enolate solution was stirred at -78°C for another 30 min. and quenched with phenylselenenyl chloride (210mg, 1.1mmol) in dry THF (4ml). After warming to room temperature (3h), the reaction mixture was diluted with brine (10ml) and

extracted with ether (3 x 20ml). The residue obtained after usual work-up was used as such in the next step. To this phenylseleno-ketone in DCM (15ml) was added pyridine (0.2ml, 2.5mmol) and 30% aqueous H_2O_2 (15 drops). After stirring for 45 min. at 10-20°C, the reaction mixture was diluted with water (10ml) and extracted with DCM (3 x 15 ml). The combined extract was washed, dried and the residue obtained after removal of solvent was charged on a silica gel (10g) column. Elution with 8% ethyl acetate-hexane furnished the enone **33** (124mg, 58%); IR(neat) : 3050, 1700, 1640, 1590, 900 cm^{-1}; ^1H NMR: δ 7.40 (1H, d, J=7Hz, -CH=CH-C=O), 5.96 (1H, d, J=7Hz, -CH=CH-C=O), 5.88-5.48 (3H, m, -CH=CH- and -CH=CH_2), 5.1-4.8 (2H, m, -CH=CH_2) 3.2-1.44 (11H, series of m); ^{13}C NMR: δ 212.5, 170.3, 138.2, 135.1, 130.9, 129.5, 114.9, 62.6, 60.2, 51.3, 47.1, 41.5, 40.0, 38.6, 30.0; Anal. Calcd. for $C_{15}H_{18}O$: C, 84.06; H,8.46. Found: C, 84.17; H,8.44.

6-(3-Oxobutyl)-tricyclo[6.3.0.0^{2,6}]undeca-4,9-dien-3-one 34: A mixture of $PdCl_2$ (60mg, 0.34mmol), CuCl (500mg, 5mmol) dimethylformamide (10ml) and water (3ml) was stirred under oxygen blanket for 1h. To this activated mixture, the enone **33** (300mg, 1.4mmol) in dimethylformamide (5ml) was added and stirring continued for 3h at room temperature. The reaction mixture was quenched by adding 10% HCl (5ml) and extracted with ether (3 x 20 ml). The residue obtained after work-up was charged on a silica gel (10g) column. Elution with 20% ethylacetate-hexane furnished the keto-enone **34** (260mg, 80%); IR(neat): 3050,1700,1590 cm^{-1}; ^1H NMR: δ 7.32 (1H, d, J=6Hz, -CH=CH-C=O), 5.94 (1H, d, J=6Hz, -CH=CH-C=O), 5.72-5.48 (2H, m, -CH=CH-) 3.16-1.44 (11H, series of m), 2.06 (3H, s, -C-CH_3); ^{13}C NMR: δ 212.2, 207.8, 169.8, 134.9, 131.0, 129.4, 62.0, 59.3, 51.2, 46.8, 41.3, 39.8, 39.5, 31.9, 29.8; Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.87. Found: C, 77.85; H, 7.90.

Tetracyclo[7.6.0.0^{1,6}.0^{10,14}]pentadec-12-en-4,8-dione 35: Sodium hydride (160mg, 3.3mmol; 50% dispersion in mineral oil) was placed in a RB flask under N_2 blanket. Dry THF (8ml) was introduced, followed by keto-enone **34** (180mg, 0.78mmol) in dry THF (5ml). The reaction mixture was stirred at 50°C for 2h and then carefully poured on crushed ice and extracted with ethyl acetate (3 x 15ml). The residue obtained after work-up was passed through a small silica gel column to furnish the tetracyclic diketone **35** (140mg, 78% yield); mp.: 67-68°C; IR(KBr): 3050, 1720 cm^{-1}; ^1H NMR: δ 5.74-5.5 (2H, m, -CH=CH-), 3.52-1.2 (16H, series of m); ^{13}C NMR: δ 218.9, 211.2, 135.0, 128.8, 67.1, 51.5 (2C), 44.9, 43.2, 42.3 (2C), 40.0, 39.8, 38.1, 33.5; Anal. Calcd. for $C_{15}H_{18}O_2$: C, 78.22; H, 7.87. Found : C, 77.82; H, 7.79.

3-Mesyloxymethyl4-(2-mesyloxyethyltricyclo[6.4.0.0^{1,5}]dodeca-6,10-dione bis ethylene ketal 37: A mixture of diketone **35** (100mg, 0.43mmol), ethanediol (0.07ml, 1.1mmol), *p*-toluenesulfonic acid (5mg) and benzene were placed in an RB flask fitted with a Dean-Stark water separator. The contents were refluxed for 2h and the reaction was worked-up in usual fashion to furnish the corresponding *bis*-ketal (120mg, 88%) as a syrupy liquid; IR(neat): 3050, 1445, 1190 cm^{-1}; ^1H NMR: δ 5.7-5.42 (2H, m -CH=CH-), 4.08-3.7 (8H, m), 3.4-1.18 (16H, series of m); Anal. Calcd. for $C_{19}H_{26}O_4$: C, 71.66; H, 8.22; Found: C, 71.05; H, 8.16. Into a solution of the above olefinic *bis*-ketal (100mg, 0.31mmol) in methanol (15ml) at -78°C was bubbled ozone until blue color appeared. Excess ozone was flushed out with a slow stream of N_2 and sodium borohydride (47mg, 1.24mmol) in small portions was added. The reaction mixture was allowed to warm to room temperature and acetone (0.1ml) was added. Methanol was removed, the residue was diluted with water (5ml) and extracted with chloroform (4 x 10 ml) to furnish the crude diol **36**. To the crude diol **36** in dry DCM (10ml) was added triethylamine (0.2ml) and

methanesulfonylchloride (0.06ml, 0.78mmol) under N_2 atmosphere at -23°C. The reaction mixture was allowed to warm to room temperature and quenched by adding sat.NaHCO3 solution. The contents were extracted with DCM (3 x 10 ml), washed and dried. The residue was charged on a silica gel (5g) column. Elution with 60% ethyl acetate-hexane furnished the bis-ketal dimesylate **37** (120mg, 75% from 62) as a syrupy liquid; IR(neat): 2950, 1440, 1350, 1160 cm^{-1}; ^1H NMR: δ 4.36-4.08 (4H, m, $(-CH_2-OMs)_2$), 3.96-3.76 (8H, br s), 3.02 (3H, s), 3.00 (3H, s), 2.76-1.20 (16H, series of m); Anal. Calcd. for $C_{21}H_{34}O_{10}S_2$: C, 49.47; H, 6.71. Found: C, 49.70; H, 6.62.

5-Methyl-5-azatetracyclo[7.7.0.0^{3,8}.0^{1,12}]hexadecan-10,14-dione 38 Into a solution of dimesylate **37** (210mg, 0.41mmol) in dry dimethylsulfoxide (12ml) in a thick-walled tube was bubbled a gentle stream of methylamine at 15°C. The tube was sealed and placed in an oil bath at 85-90°C for 16h. The sealed tube was cooled to 0°C, opened carefully and the reaction mixture was poured into water (25ml). Extraction with DCM (3 x 20ml),washing and drying furnished a residue which was filtered through a short basic alumina column to furnish the cyclized N-methylpiperidine *bis*-ketal derivative (108mg, 75% yield) as a syrupy liquid; IR(neat): 2900, 2750, 1100 cm^{-1}; ^1H NMR: δ 4.08-3.72 (8H, m), 2.68-1.28 (20H, series of m), 2.22 (3H, s -N-CH_3); ^{13}C NMR: δ 116.9, 108.8, 64.6, 64.3, 64.1 (2C), 63.5, 57.2, 55.2, 49.2, 46.8, 41.6, 41.1, 39.3, 38.8, 36.2, 34.9, 33.0, 32.1, 28.8; Mass: $C_{20}H_{31}NO_4$. Calcd.: 349. Found: 349. Anal. Calcd. for $C_{20}H_{31}NO_4$: C, 68.73; H, 8.94; N, 4.00. Found: C, 69.01; H, 8.98; N, 3.88.

To a solution of the above tetracyclic *bis*-ketal (30mg, 0.085mmol) in THF (3ml), 15% hydrochloric acid (0.2ml) was added and the contents were stirred at room temp. for 1h. The reaction mixture was made alkaline by adding 5% NaOH solution (0.6ml) and extracted with ethyl acetate (3 x 10 ml). The residue obtained after the removal of solvent was passed through a short basic alumina column to furnish the diketone **38** (11.2mg, 50% yield) which was crystallized from DCM-hexane; mp: 103-104°C; IR(KBr): 2950, 2740, 1735, 1710 cm^{-1}; ^1H NMR: δ 3.06-1.56 (20H, series of m), 2.26 (3H, s, -N-CH_3); ^{13}C NMR: δ 218.3, 211.6, 63.5, 56.8, 54.1, 48.6, 46.6, 45.8, 42.1, 42.0, 41.5, 40.1, 39.0, 37.5, 35.0, 27.7. Anal. Calcd. for $C_{16}H_{23}NO_2$: C, 73.52; H, 8.87; N, 5.35. Found: C, 73.68; H, 8.91; N, 5.32. HRMS: $C_{16}H_{23}NO_2$: Calcd.: 261.1729. Found: 261.1749.

5-Methyl-14-methylene-5-azatetracyclo[7.7.0.0^{3,8}.0^{1,12}]hexadecan-10-one 41: To a stirred suspension of methyltriphenylphosphonium bromide (107mg, 0.3mmol) in dry benzene (15ml), sodium *t*-amyl oxide (18mg, 0.16mmol) in dry benzene (0.5ml) was added under N_2. The ylide solution was stirred at room temperature for 20min and the diketone **38** (35mg, 0.134mmol) in benzene (5ml) was added. The reaction mixture was stirred for another 10 min. and quenched by adding water (5ml). The reaction mixture was extracted with ethyl acetate (2 x 10 ml) washed and dried. The residue obtained after the removal of solvent was charged on a basic alumina (5g) column. Elution with 50% ethyl acetate-hexane furnished the monomethylenated ketone **41** (27mg, 78%); IR(neat): 3050, 2900, 2760, 1730, 1640, 890 cm^{-1}; ^1H NMR: δ 4.86 (1H, br s), 4.68 (1H, br s), 2.56-1.48 (20H, series of m), 2.24 (3H, s, N-CH_3); ^{13}C NMR: δ 219.9, 144.8, 110.0, 62.9, 57.9, 52.6, 49.4, 46.7, 43.5, 42.6, 40.9, 40.3, 38.8, 37.1, 33.7, 32.0, 26.6. Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.71; N, 5.39. Found: C, 78.89; H, 9.76; N, 5.42.

Acid catalyzed isomerization of 41 to deoxy7magellaninone 32: To a stirred solution of monomethylenated ketone **41** (32mg, 0.123mmol) in dry benzene (10ml) was added *p*-toluenesulfonic acid (30mg, 0.15mmol) and the contents refluxed for 6h. The reaction mixture

was cooled and poured into sat.$NaHCO_3$ solution (5ml). Extraction with ethyl acetate (2 x 10 ml), washing and drying furnished a residue which was passed through a small basic alumina column to yield the endocyclic olefin **32** (26mg, 81.25%) as a gummy material; IR(neat): 2950, 2760, 1730 cm^{-1}; ^1H NMR (500 MHz): δ 5.38 (1H, br s, -C=CH-), 2.72-1.5 (18H, series of m), 2.28 (3H, s, -N-CH_3), 1.68 (3H, br s, -CH=C-CH_3); ^{13}C NMR: δ 219.8, 135.1, 121.8, 63.9, 57.8, 54.4, 47.8, 46.7, 45.9, 41.8, 40.7, 39.6, 38.9, 33.1, 28.2, 28.1, 23.6. Anal. Calcd. for $C_{17}H_{25}NO$: C, 78.71; H, 9.71; N, 5.39. Found: C, 78.45; H, 8.68; N, 5.34.

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