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Synthetic Approaches to the Manumycin A, B and C Antibiotics: The First Total Synthesis of (+)-Manumycin A‡

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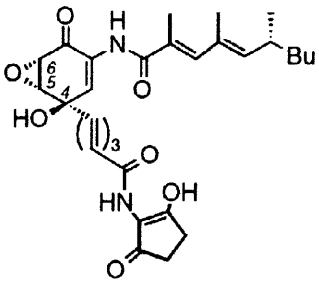
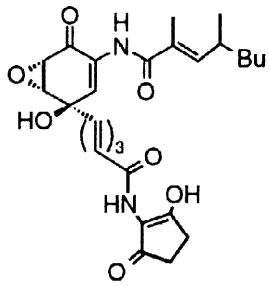
Abstract: The first total synthesis of Manumycin A, as its (+)-enantiomer, is reported. The synthetic route features an asymmetric epoxidation (based on Wynberg's chiral phase transfer methodology) for the preparation of the key epoxyquinol nucleus, and a further demonstration of the utility of the Stille reaction for the construction of the Manumycin lower side chain. This synthesis of Manumycin A corrects the original stereochemical assignment and confirms the *syn*-hydroxy epoxide arrangement. The first syntheses of the quinones obtained by the oxidative degradation of Manumycins A-C are also described.

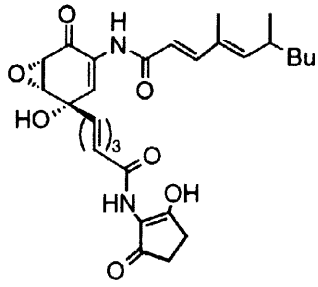
In 1963, Buzzetti, Prelog and colleagues described the isolation of a novel, yellow crystalline antibiotic from *Streptomyces parvulus* (Tü 64) found in soil samples collected in Manchester, England. They christened the compound Manumycin (later Manumycin A) and reported preliminary spectroscopic studies.[1] Subsequent research was carried out by Zeeck's group in Göttingen, and in 1973 they described elegant degradation and spectroscopic studies which resulted in the elucidation of the novel structure of Manumycin A, although assignment of the stereochemistry of the four chiral centres was not possible.[2] The seminal publications in this area, again by Zeeck's group, appeared in 1987.[3] Meticulous degradation and NMR studies confirmed the gross structure of Manumycin A together with the alkene stereochemistries. Degradation products were also utilised to determine the absolute configuration of the side chain methyl substituent and, by CD comparison with related natural products, the epoxide configuration as 5*R*,6*S*. The final stereocentre, C-4, was assigned as 4*R* using the exciton chirality CD procedure originally utilised for Asukamycin,[4] giving the structure of Manumycin A as **1**.



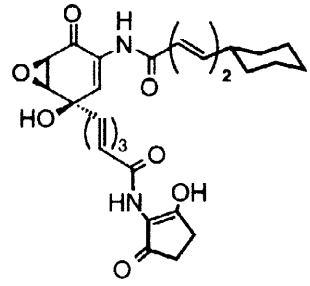
Manumycin A **1**
(Original structure)



Manumycin B **2**
(Original structure)



Manumycin C **3**



Alisamycin **4**

‡*In memory of Professor Sir Derek Barton.*

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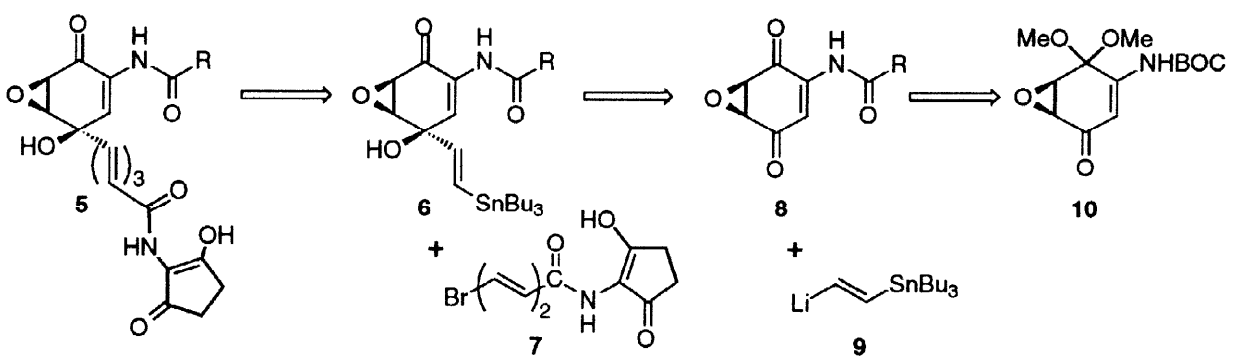
In structural terms, Manumycin A represented a new antibiotic type, but before long related analogues were discovered (*e.g.* Asukamycin,[4] Manumycin B **2**,[5] Manumycin C **3**[5] and Alisamycin **4**[6]).[7,8] In addition, the closely related dihydroxycyclohexenones Manumycin D and TMC-1 A-D have also been described.[5,9] Two stereochemical points are worthy of note. Firstly, both enantiomeric series of epoxycyclohexanes are represented: Manumycin A **1** and most other members have the 5*R*,6*S*-configuration whereas Alisamycin **4** has the 5*S*,6*R*-configuration. Secondly, and more surprisingly, the hydroxy-epoxide moiety is apparently found in both *syn*- and *anti*-orientations. Thus, for example, Manumycin A **1** and Manumycin B **2** have been assigned the *anti*-geometry whereas most of the other members of the family (including Manumycin C **3** and Alisamycin **4**) are *syn*-hydroxy epoxides. This difference has attracted recent attention in terms of its biosynthetic origin:[10] it has been pointed out that the dioxygenase mechanism of phenol oxidation would lead to the formation of *syn*-hydroxy epoxides. Other observations also raise doubts about the validity of the original stereochemical assignment given to C-4 of Manumycin A. For example, extensive NMR studies on Manumycin D have recently confirmed the C-4 stereochemistry as *S*. This seems surprising if the 4*R*-configuration of Manumycin A is correct, particularly as Manumycins A and D occur as co-metabolites.[5,9] In addition, our own studies with Manumycin analogues lacking the lower side chain,[8] or with saturated lower chains,[11] indicate that *syn*- and *anti*-hydroxy epoxide diastereoisomers would be expected to exhibit very different ^{1}H-NMR characteristics, particularly for H-3 and H-5: in contrast, published data for Manumycin members of the *syn*- and *anti*-series are remarkably similar.[3,5]

The Manumycin family are of interest, not only because of their unique and exquisite structures, but also because of their potentially useful biological properties.[10b] In addition to antibacterial activity, insecticidal, antifungal, anticoccidial and cytotoxic activities have been reported, as have inhibitory activity against polymorphonuclear elastase and human interleukin-1β converting enzyme. Perhaps of greatest significance, however, is the discovery that Manumycins A-C act as selective inhibitors of the enzyme Ras protein farnesyl transferase and thus have potential as anti-cancer agents.[12]

The development of a synthetic route to the Manumycin family, and the clarification of the structural uncertainties, is thus of great importance from both a biosynthetic and a pharmaceutical standpoint. The only reported preparation of a member of the Manumycin family bearing the complete unsaturated lower side chain is our synthesis of Alisamycin **4**,[8,13] which is shown in retrosynthetic form in Scheme 1.

Scheme 1



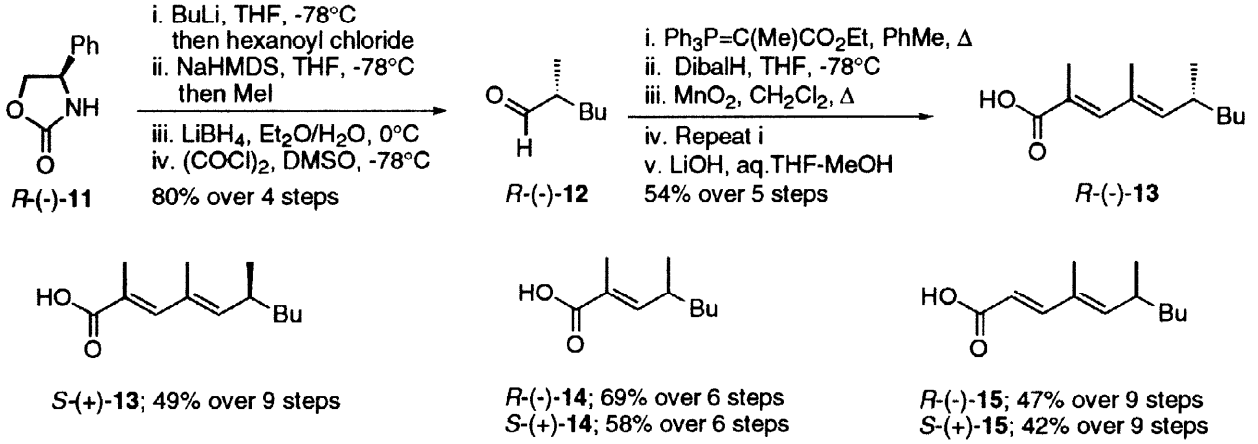
This approach utilises the Stille cross coupling reaction[14] between **6** and **7**[15] to construct the key lower side chain in **5**. It should be noted that: (i) the key organometallic addition reaction to produce **6** from **8** and **9** proceeds stereoselectively to give the *syn*-hydroxy epoxide adduct,[8] and so would lead to "*syn*-Manumycin A"; (ii) the epoxide starting material **10** is readily obtained[13,16] as the (-)-5*S*, 6*R*-enantiomer (Manumycin numbering) using Wynberg's chiral phase transfer epoxidation procedure,[17] and so would produce *ent*-Manumycins. Herein, we report the first total syntheses of the quinones **8** obtained from the oxidative degradation of Manumycins A-C, and thereby establish that their reported structures are correct. We then

describe the use of *ent*-Manumycin A quinone in the first total synthesis of *ent*-(+)-Manumycin A, and confirm that it is indeed a *syn*-hydroxy epoxide,[16] in contrast to the published structure.[3]

Preparation of the upper side chain acids

The upper side chain acids **13**, **14** and **15** of Manumycin A, B and C respectively were prepared, in both enantiomeric forms, using Evans' chiral oxazolidinone methodology[18] (Scheme 2). Thus, *R*-4-phenyloxazolidinone **11**[18b] was converted *via* a modified[18c] literature route into the known aldehyde *R*-(-)-**12**[19] in 4 steps (*ca.* 80% overall). A double Wittig chain extension sequence followed by saponification gave the Manumycin A side chain *R*-(-)-**13** which gave data fully consistent with the acid isolated by degradation of the natural compound.[3] A similar sequence commencing from *S*-**11** gave *S*-(+)-**13**, the acid needed for the preparation of *ent*-Manumycin A. The side chains **14** and **15**, in both enantiomeric forms, were prepared in a similar manner.

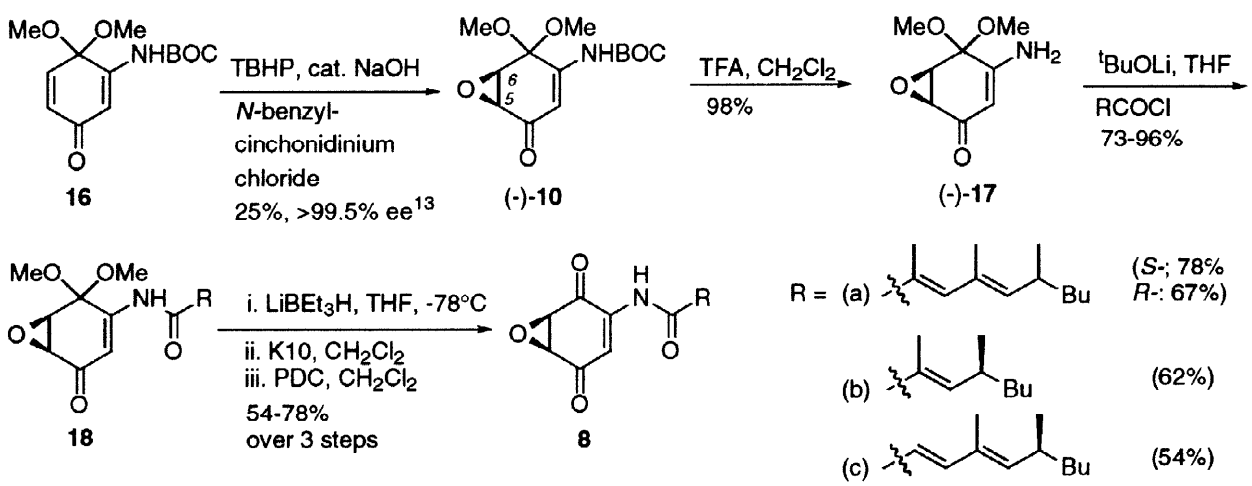
Scheme 2



Preparation of the Manumycin quinones 8

The retrosynthetic analysis (Scheme 1) proceeds *via* quinones **8**. These quinones were also obtained during the Manumycin structure elucidation studies and so their synthesis would provide confirmation of the proposed structures. The synthetic route[13] to quinones **8** is illustrated in Scheme 3.

Scheme 3



Firstly, we had to find an efficient way to convert the readily-available[8] dienone **16** into the key epoxide **10** in enantiomerically pure form.[13,16,20] We utilised a modified[13] version of Wynberg's chiral phase transfer catalysis procedure[17] (Scheme 3). The optimum procedure involved the use of one molar equivalent of *N*-benzylcinchonidinium chloride and TBHP in toluene with catalytic sodium hydroxide giving the desired epoxide (-)-**10** in 32% yield (82% based on recovered **16**) and high e.e. (89%). To our knowledge, this is the highest e.e. ever obtained for the epoxidation of cyclohexenones using chiral phase transfer catalysis. Two recrystallisations of the reaction product from dichloromethane-hexane gave enantiomerically pure (-)-**10** (> 99.5% as determined by HPLC on a Chiralcel OJ column).

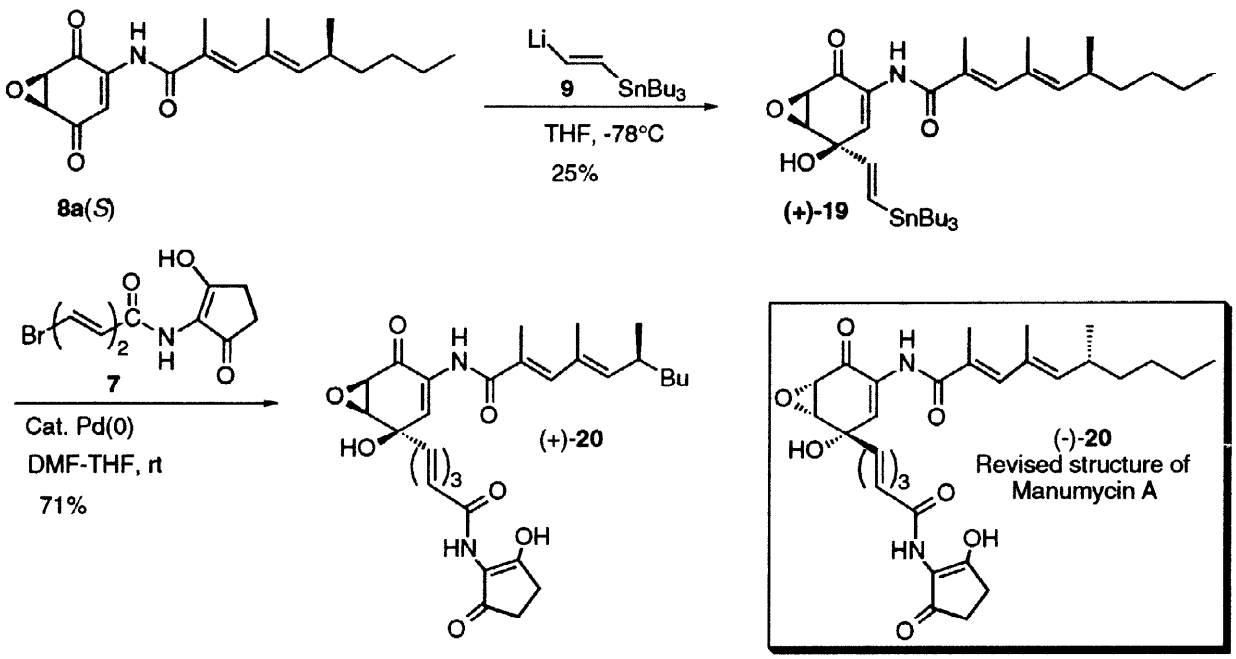
The predominant (-)-enantiomer was assigned the 5*S*, 6*R*-configuration (Manumycin numbering) by analogy with Wynberg's assignment to cyclohexenone oxide produced by similar procedures[17a] and by conversion into the known compounds (-)-Alisamycin quinone and (+)-MT 35214.[13] We had hoped, based on literature precedent,[17b] that the pseudoenantiomeric *N*-benzyl cinchoninium chloride would give a predominance of (+)-**10** but, under the optimum conditions, its use again gave (-)-**10**, albeit in only 10% e.e. The 5*S*, 6*R*-(-)-enantiomer of **10** obtained in this study is the appropriate precursor for the preparation of Alisamycin **2**[13] but the 5*R*, 6*S*-(+)-enantiomer is required for the synthesis of natural Manumycins. We decided, however, to proceed with (-)-**10** and thus prepare *ent*-Manumycins (Schemes 3 and 4).

The BOC protecting group was removed by treatment with TFA and the resulting crystalline amine (-)-**17** was acylated (*t*-BuOLi, THF) with the acid chlorides prepared from the (*S*)-enantiomers of **13-15** using oxalyl chloride. The resulting amides **18** were stereoselectively reduced to the corresponding *syn* secondary alcohols using superhydride ($LiBEt_3H$), the dimethoxyacetal removed using Montmorillonite K10,[21] and the alcohols re-oxidised to produce quinones **8** in reasonable overall yield. The data obtained for quinones **8b** and **8c** were entirely consistent with those reported[22] for the enantiomeric compounds, thereby confirming the published structural assignments for these degradation products of Manumycin B and Manumycin C and establishing the configuration of the side chain methyl substituents. The spectroscopic data for **8a**(*S*) were also consistent with published[3] values for the Manumycin A derived quinone but its optical rotation was close to zero {Lit.[3] $[\alpha]_D$ -8.0 for the enantiomer}. We established that **8a**(*S*) is indeed the enantiomer of the Manumycin A by carrying out CD studies [found: 372 nm (-7.47), 322 (+12.63), 249 (-4.14), 228 (+9.18); lit.[3] 362 nm (+7.76), 312 (-13.4), 242 (+4.41), 218 (-8.82)], and by preparing the diastereoisomeric quinone **8a**(*R*) {$[\alpha]_D$ -149.8 (*c* 1.5, $CHCl_3$)}. These results therefore confirm the absolute stereochemistry of the epoxide moiety of Manumycins A-C, initially proposed on the basis of comparative CD studies,[3,22] and establish that the *R*-configuration of the side chain methyl group (already confirmed for Manumycin A)[3] is also present in Manumycins B and C.

Preparation of (+)-Manumycin A 20

With quinone **8a**(*S*) in hand, we were able to complete the first synthesis of Manumycin A as its (+)-enantiomer (Scheme 4). Addition of vinyllithium reagent **9**[23] to quinone **8a** gave a mixture of products from which (+)-**19** was obtained as the major adduct in 25% yield after chromatography. The assignment of the *syn*-hydroxy epoxide stereochemistry was based on precedent: complete stereoselectivity for organometallic attack from the face opposite the epoxide has been observed in a number of closely related examples. In addition, NMR data for (+)-**19** was consistent those of related *syn*-hydroxy epoxides,[8,11] one of which was characterised by X-ray crystallography.[8] Stannane (+)-**19** was then coupled to the bromodiene **7**[15] using Negishi's Pd(0) catalyst [5% $PdCl_2(Ph_3P)_2$, DibalH][24] to give (+)-**20** in 71% yield as a bright yellow solid (m.p. 134-136°C lit.[3] m.p. for (-)-Manumycin A, 139-141°C dec.). The spectroscopic and chromatographic data (500 MHz ^1H NMR, 125 MHz ^{13}C NMR, IR, UV, low and high resolution FAB MS, TLC) were entirely consistent with the literature[3] values for Manumycin A and with those obtained from authentic samples.[25] The degree of coincidence between this data is such that we believe the case for Manumycin A possessing the *syn*-hydroxy epoxide structure with the 4*S*-configuration is now overwhelming.

Scheme 4



The optical rotation obtained for (+)-**20** is also consistent with the value obtained from an authentic sample {$[\alpha]_D$ +193.0 (*c* 0.1, $CHCl_3$); $[\alpha]_D$ (commercial)[25] -191.4 (*c* 0.7, $CHCl_3$)} and the CD data also provides convincing evidence that (+)-**20** is the enantiomer of natural Manumycin A. This study therefore indicates that the structure of naturally occurring Manumycin A should be revised to (-)-**20**.

The assignment of C-4 stereochemistry to the Manumycin family of natural products using the exciton chirality procedure was based on the conclusion that a positive CD couplet indicates the presence of a 4*S*-stereocentre, a negative couplet a 4*R*-stereocentre.[3,4,5,26] However, it should be noted that (+)-**20** exhibits a positive CD couplet but, from its method of synthesis, has the 4*R*-configuration. It would therefore appear that variations in the substitution pattern of the upper side chain can result in exceptions to this exciton chirality rule, presumably due to conformational changes resulting in a realignment of the coupled chromophores. Caution should therefore be applied when using CD to assign the C-4 stereochemistry to new members of this family of natural products. It also seems likely that the structures of Manumycins B **2**[5] and E-1625-2,[26] which were also assigned as *anti*-hydroxy epoxides by use of the exciton chirality method, will need to be revised to the corresponding *syn*-hydroxy-epoxide structures (*i.e.* with 4*S*- rather than 4*R*-configurations).

In summary, the first total synthesis of Manumycin A, as its (+)-enantiomer **20**, has thus been achieved, leading to a revision of the published structure of the natural product. The revised *syn*-hydroxy epoxide stereochemistry is now consistent with the biosynthetic mechanism proposed by Gould, Floss *et al.*[10] Quinones **8b** and **8c** constitute ideal precursors for the synthesis of Manumycins B and C using the methododology described above. This synthetic route is also suitable for the preparation of a range of novel Manumycin analogues for structure-activity studies. This research is underway and will be reported in due course.

EXPERIMENTAL

General Directions

Detailed general directions can be found in reference 15b. Aldehyde *R*-(-)-**12**[19] was prepared from *R*-4-phenyloxazolidinone **11**[18b] in 4 steps (*ca.* 80% overall) following a published procedure.[18c] A similar sequence commencing from *S*-**11** gave *S*-(+)-**12**. Epoxide (-)-**10**[8,13] and bromodiene **7**[15b] were prepared using published procedures.

Representative Procedure for the Preparation of Side Chain Acids 13-15:
(2*E*,4*E*,6*R*)-2,4,6-Trimethyldeca-2,4-dienoic acid *R*-(-)-13

(a) (Carboethoxyethylidene)triphenylphosphorane (6.9 g, 19 mmol) was added to a solution of *R*-(-)-2-methylhexanal **12** (1.1 g, 9.6 mmol) in toluene (50 mL) under nitrogen. The mixture was boiled under reflux for 2 h, then cooled to rt, filtered through silica (20 g, ether), the solvent evaporated *in vacuo* and the residue chromatographed (ether-hexanes, 1:9) to give ethyl (2*E*, 4*R*)-2,4-dimethyloct-2-enoate (1.61 g, 84%) as a colourless oil, R_f 0.43 (Et_2O-PE, 9:1); $[\alpha]_D$ -31.5 (*c* 2.4, $CHCl_3$) which was fully characterised.

(b) A solution of DibalH (1.0 *M* in hexanes, 12.6 mL, 12.6 mmol) was added dropwise over 5 min to a solution of the above ester (1.0 g, 5.0 mmol) in THF (20 mL) at -78°C, the mixture was stirred for 3 h, then warmed to -20°C. Methanol (5 mL) was added cautiously, and the solution was poured into sodium tartrate (20% aq., 40 mL) and the resulting mixture was stirred vigorously for 2 h. An ether work-up (2 x 30 mL), incorporating a brine (30 mL) wash, followed by chromatography (ether-hexanes, 1:8) gave (2*E*, 4*R*)-2, 4-dimethyloct-2-en-1-ol (0.78 g, 99%) as a colourless liquid, R_f 0.15 (Et_2O-PE, 1:4); $[\alpha]_D$ -17.0 (*c* 1.5, $CHCl_3$) which was fully characterised.

(c) A solution of the above allylic alcohol (0.75 g, 4.8 mmol) in DCM (50 mL) was heated under reflux with manganese dioxide (6.3 g, 72.5 mmol) for 2 h. The suspension was then filtered through a pad of Celite and the filtrate evaporated *in vacuo* to give (2*E*, 4*R*)-2, 4-dimethyloct-2-enal (710 mg, 96%) as a colourless liquid, R_f 0.46 (Et_2O-PE, 1:4); $[\alpha]_D$ -18.9 (*c* 1.8, $CHCl_3$) which was fully characterised.

(d) A solution of the above aldehyde (345 mg, 2.24 mmol) and (carbethoxyethylidene)triphenylphosphorane (1.65 g, 4.55 mmol) were heated under reflux in toluene (25 mL) for 3 h. The solvent was removed *in vacuo* and the residue chromatographed (Et_2O-PE, 5:95) to give ethyl (2*E*, 4*E*, 6*R*)-2,4,6-trimethyldeca-2,4-dienoate (415 mg, 78%) as a colourless oil, R_f 0.55 (Et_2O-PE, 1:4); $[\alpha]_D$ -56.8 (*c* 1.5, $CHCl_3$) which was fully characterised.

(e) Lithium hydroxide monohydrate (613 mg, 14.7 mmol) in water (1.6 mL) was added to a solution of the above ester (350 mg, 1.47 mmol) in THF (3 mL) and methanol (1.6 mL) and the mixture was stirred for 24 h at rt. The pH was adjusted to 1.0 by addition of 10% aq. HCl, and the cloudy solution extracted with DCM (2 x 30 mL). The solution was dried ($MgSO_4$) and evaporation of the solvent *in vacuo* followed by chromatography (EtOAc-PE, 1:1) to give the title compound *R*-(-)-**13** (265 mg, 86%) as a colourless oil, R_f 0.57 (EtOAc-PE, 1:1); $[\alpha]_D$ -76.3 (*c* 1.9, $CHCl_3$) [Lit.[3] -75.8 (*c* 1.6, $CHCl_3$)] which was fully characterised and had data consistent with those published.[3]

Acids *S*-(+)-13, *S*-(+)-14 and *S*-(+)-15

Using procedures similar to those described above *S*-(-)-2-methylhexanal **12** was converted into *S*-(+)-**13**, *S*-(+)-**14** and *S*-(+)-**15**:

(2*E*,4*E*,6*R*)-2,4,6-Trimethyldeca-2,4-dienoic acid *S*-(+)-13 as a colourless oil (60% over 5 steps): $[\alpha]_D$ +74.3 (*c* 2.3, $CHCl_3$). Other data as published for *R*-(-)-13.[3]

(2*E*,4*S*)-2,4-Dimethyloct-2-enoic acid *S*-(+)-14 as a colourless oil (58% over 2 steps), R_f 0.55 (EtOAc-PE, 1:1); δ_H ($CDCl_3$, 500 MHz) 6.70 (1 H, dq, *J* 10.1, 1.3 Hz), 2.55-2.49 (1 H, m), 1.84 (3 H, d, *J* 1.3 Hz), 1.44-1.19 (6 H, m), 1.01 (3 H, d, *J* 6.7 Hz), 0.88 (3 H, t, *J* 7.2 Hz); δ_C ($CDCl_3$, 67.5 MHz) 174.2, 151.1, 125.6, 36.4, 33.4, 29.6, 22.7, 19.8, 14.0, 12.0; ν_{max} (film) 2958, 2927, 2860, 1687, 1643, 1456, 1421, 1273 cm^{-1}; *m/z* (EI) 170 (M^+, 10%) [Found: M^+, 170.13112. $C_{10}H_{18}O_2$ requires 170.13068 (2.6 ppm error)]; $[\alpha]_D$ +37.6 (*c* 1.0, $CHCl_3$).

(2*E*,4*E*,6*S*)-4,6-Dimethyldeca-2,4-dienoic acid *S*-(+)-15 as a as a colourless oil (55% over 5 steps), R_f 0.54 (EtOAc-PE, 1:1); ^1H NMR ($CDCl_3$, 500 MHz) δ_H 7.42 (1 H, d, *J* 15.5 Hz), 5.79 (1 H, d, *J* 15.5 Hz), 5.74 (1 H, d, *J* 10.0 Hz), 2.60-2.50 (1 H, m), 1.80 (3 H, s), 1.45-1.20 (6 H, m), 0.99 (3 H, d, *J* 7.0 Hz), 0.88 (3 H, t, *J* 7.2 Hz); δ_C ($CDCl_3$, 67.5 MHz) 173.2, 152.4, 150.2, 131.3. 114.6, 36.9, 33.3, 29.7, 22.8, 20.4, 14.0, 12.3; ν_{max}

(film) 2959, 2926, 2871, 1688, 1618, 1416, 1304, 1281, 1207, 983 cm^{-1}; *m/z* (EI) 196 (M^+, 3%) [Found: M^+, 196.14723. $C_{12}H_{20}O_2$ requires 196.14633 (4.6 ppm error)] ; $[\alpha]_D$ +57.5 (*c* 1.5, $CHCl_3$).

3-Amino-4,4-dimethoxy-5,6-epoxycyclohex-2-en-1-one (-)-17

Epoxide (-)-**10**[8,13] (1.04 g, 3.65 mmol) and anisole (0.8 mL) were dissolved in dry DCM (42 mL) and the mixture stirred at rt. Trifluoroacetic acid (10.5 mL) was slowly added over a period of 10 min, and the solution turned green. Stirring was continued for 1 h after which the solvent was removed *in vacuo*. Chromatography (EtOAc) gave the title compound (-)-**17** (660 mg, 98%) as a white solid, m.p. 162-163°C; R_f 0.30 (EtOAc); $[\alpha]_D$ -91 (*c* 1, MeOH) with other data consistent with those published for the racemic material.[8]

Representative Procedure for the Preparation of Amides 18: Amide 18a(*S*)

(a) Oxalyl chloride (34 μL, 0.39 mmol) was added slowly over 5 min to a stirred solution of acid *S*-(+)-**13** (74 mg, 0.352 mmol) at 0°C in DCM (2.5 mL) containing 1 drop of dimethylformamide. The reaction was then stirred for 1 h at rt. Removal of the solvent *in vacuo* gave the acid chloride (80 mg, *ca.* 100%) which was used in the next step without further purification

(b) A solution of lithium *tert*-butoxide (1.0 *M* solution in THF, 360 μL, 0.36 mmol) was added dropwise over 15 min to a stirred solution of amine (-)-**17** (60 mg, 0.32 mmol) in dry THF at 0°C under nitrogen. After stirring at 0°C for 30 min, a solution of the acid chloride prepared from from *S*-(+)-**13** as in (a) (80 mg, 0.35 mmol) in THF (1 mL) was added dropwise over 1 h. The reaction was allowed to warm to rt and stirred until acylation was complete by TLC analysis (2-3 h). Satd. aq. NH_4Cl was then added followed by EtOAc and water. The two layers were separated and the aqueous layer extracted with EtOAc. The combined organic layers were dried ($MgSO_4$) and the solvent removed *in vacuo*. The dark oily residue was purified by chromatography (EtOAc-hexanes, 3:7) to obtain amide **18a**(*S*) as a colourless oil (111 mg, 91%), R_f 0.59 (EtOAc-PE, 1:1); δ_H ($CDCl_3$, 500 MHz) 8.11 (1 H, s), 7.21 (1 H, d, *J* 2.0 Hz), 6.79 (1 H, br s), 5.36 (1 H, br d, *J* 9.5 Hz), 3.84 (1 H, d, *J* 4.0 Hz), 3.68 (3 H, s), 3.53 (1 H, dd, *J* 2.0, 4.0 Hz), 3.32 (3 H, s), 2.51-2.42 (1 H, m), 2.06 (3 H, d, *J* 1.5 Hz), 1.83 (3 H, d, *J* 1.5 Hz), 1.43-1.15 (6 H, m), 0.99 (3 H, d, *J* 7.0 Hz), 0.89 (3 H, t, *J* 7.0 Hz); δ_C ($CDCl_3$, 125 MHz) 192.8, 168.4, 145.5, 143.3, 141.0, 129.9, 128.3, 108.5, 95.8, 52.2, 51.5, 51.4, 50.9, 37.0, 32.9, 29.8, 22.8, 20.6, 16.5, 14.0, 13.9; ν_{max} (film) 3411, 2956, 2927, 2870, 1695, 1674, 1622, 1500, 1234, 1214, 1122, 1058 cm^{-1}; *m/z* (CI) 378 (MH^+, 100%), 346 (M - OMe, 24) [Found: MH^+, 378.22732. $C_{21}H_{32}NO_5$ requires 378.22805 (1.9 ppm error)]; $[\alpha]_D$ -126.8 (*c* 1.0, $CHCl_3$).

Amides 18a(*R*), 18b and 18c

These compounds were prepared following the representative procedures described above:

Amide 18a(*R*) as a colourless oil (96%), R_f 0.52 (EtOAc-DCM, 5:95); δ_H ($CDCl_3$, 500 MHz) 8.11 (1 H, s), 7.18 (1 H, d, *J* 2.1 Hz), 6.78 (1 H, br s), 5.35 (1 H, br d, *J* 9.7 Hz), 3.83 (1 H, d, *J* 4.2 Hz), 3.67 (3 H, s), 3.52 (1 H, dd, *J* 2.1, 4.2 Hz), 3.31 (3 H, s), 2.49-2.42 (1 H, m), 2.05 (3 H, d, *J* 1.3 Hz), 1.82 (3 H, d, *J* 1.2 Hz), 1.40-1.20 (6 H, m), 0.97 (3 H, d, *J* 6.7 Hz), 0.88 (3 H, t, *J* 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ_C 192.7, 168.2, 145.4, 143.1, 140.8, 129.8, 128.2, 108.3, 95.7, 52.0, 51.4, 51.2, 50.7, 36.9, 32.8, 29.7, 22.7, 20.5, 16.4, 14.0, 13.9; ν_{max} (film) 3409, 2956, 2927, 2857, 1668, 1619, 1500, 1229, 1232, 1213, 1122, 1058 cm^{-1}; *m/z* (CI) 378 (MH^+, 100%), 364 (10), 346 (M - OMe, 40) [Found: MH^+, 378.22842. $C_{21}H_{32}NO_5$ requires 378.22805 (1 ppm error)]; $[\alpha]_D$ -194.7 (*c* 1.5, $CHCl_3$).

Amide 18b as a colourless oil (73%), R_f 0.52 (DCM-EtOAc, 95:5); δ_H ($CDCl_3$, 500 MHz) 8.08 (1 H, s), 7.15 (1 H, d, *J* 2.1 Hz), 6.18 (1 H, dq, *J* 9.8, 1.4 Hz), 3.83 (1 H, d, *J* 4.2 Hz), 3.66 (3 H, s), 3.50 (1 H, dd, *J* 2.1, 4.2 Hz), 3.30 (3 H, s), 2.52-2.43 (1 H, m), 1.88 (3 H, d, *J* 1.4 Hz), 1.42-1.14 (6 H, m), 1.00 (3 H, d, *J* 6.6 Hz), 0.87 (3 H, t, *J* 7.3 Hz); δ_C ($CDCl_3$, 125 MHz) 192.8, 167.6, 145.41, 145.39, 129.5, 108.2, 95.7, 52.1, 51.3, 51.2, 50.8, 36.5, 33.2, 29.6, 22.7, 20.0, 13.9, 12.5; ν_{max} (film) 3409, 2957, 2928, 2870, 2856, 1692, 1669, 1626,

1502, 1463, 1231, 1210, 1123, 1058 cm^{-1}; *m/z* (CI) 338 (MH^+, 100%), 324 (25), 306 (M - OMe, 70); [Found: MH^+, 338.19645. $C_{18}H_{28}NO_5$ requires 338.19675 (0.9 ppm error)]; $[\alpha]_D$ -107.2 (*c* 1.0, $CHCl_3$).

Amide 18c as a colourless oil (75%), R_f 0.55 (DCM-EtOAc, 95-5); δ_H ($CDCl_3$, 500 MHz) 7.74 (1 H, s), 7.32 (1 H, dd, *J* 15.2, 0.7 Hz), 7.24 (1 H, d, *J* 2.1 Hz), 5.83 (1 H, d, *J* 15.2 Hz), 5.73 (1 H, br d, *J* 9.8 Hz), 3.82 (1 H, d, *J* 4.1 Hz), 3.66 (3 H, s), 3.51 (1 H, dd, *J* 2.1, 4.1 Hz), 3.30 (3 H, s), 2.53-2.47 (1 H, m), 1.78 (3 H, d, *J* 1.2 Hz), 1.40-1.15 (6 H, m), 0.97 (3 H, d, *J* 6.7 Hz), 0.85 (3 H, t, *J* 7.2 Hz); δ_C ($CDCl_3$, 125 MHz) 192.7, 165.2, 150.3, 149.7, 145.7, 130.9, 117.0, 108.6, 95.4, 52.0, 51.4, 51.3, 50.7, 36.8, 33.3, 29.6, 22.7, 20.3, 13.9, 12.4; ν_{max} (film) 3325, 2958, 2926, 2869, 1661, 1611, 1503, 1202, 1124, 1061 cm^{-1}; *m/z* (CI) 364 (MH^+, 100), 332 (M - OMe, 85) [Found: MH^+, 364.21193. $C_{20}H_{30}NO_5$ requires 364.21240 (1.3 ppm error)]; $[\alpha]_D$ -97.1 (*c* 1.0, $CHCl_3$).

Representative Procedure for the Preparation of Quinones 8:
2-[(2'*E*,4'*E*,6'*S*)-2,4,6-Trimethyldeca-2,4-dienamido]-5,6-epoxy-1,4-benzoquinone 8a(*S*)

(a) $LiBEt_3H$ (1.0 *M* in THF, 240 μL, 0.24 mmol) was added to a stirred solution of amide **18a**(*S*) (83 mg, 0.22 mmol) in THF at -78°C under nitrogen. After stirring for 30 min at -78°C, the solvent was removed *in vacuo* and the residue purified by chromatography (EtOAc-PE, 1:1) to give the corresponding alcohol (79 mg, 95%) as a colourless oil, R_f 0.21 (EtOAc-PE, 1:1); $[\alpha]_D$ +36.4 (*c* 1.2, $CHCl_3$) which was fully characterised.
(b) Montmorillonite K10 (50 mg) was added to the acetal from (a) (65 mg, 0.17 mmol) in DCM (2 mL) at rt. After 30 min, the solvent was removed *in vacuo* and the resulting residue was purified by chromatography (EtOAc-PE, 3:7) to give the corresponding hydroxy ketone (51 mg, 89%) as a colourless oil, R_f 0.32 (EtOAc-PE, 1:1); $[\alpha]_D$ +145.6 (*c* 1.2, $CHCl_3$) which was fully characterised.
(c) Pyridinium dichromate (76 mg, 0.2 mmol) was added to a stirred solution of the alcohol from (b) (45 mg, 0.135 mmol) in DCM (3 mL) at rt. The mixture was stirred at rt for 2 h and then directly chromatographed (EtOAc-PE, 1:4) followed by purification using preparative TLC (EtOAc-PE, 1-9) to give the *title compound* **8a**(*S*) (41 mg, 92%) as a yellow oil, R_f 0.37 (EtOAc-PE, 1-4); $[\alpha]_D$ 0 (*c* 1.4, $CHCl_3$) {Lit.[3] $[\alpha]_D$ (for enantiomer) -8.1 (*c* 1.0, $CHCl_3$)} which was which was fully characterised and had data consistent with those published.[3] Details of the CD data are given in the text.

Quinones 8a(*R*), 8b and 8c

These compounds were prepared following the representative procedures described above:

Quinone 8a(*R*) as a yellow oil (67% over 3 steps) , R_f 0.51 (EtOAc-hexanes, 3:7); δ_H ($CDCl_3$, 500 MHz) 8.28 (1 H, br s), 7.58 (1 H, dd, *J* 2.2, 1.1 Hz), 6.84 (1 H, br s), 5.40 (1 H, br d, *J* 9.7 Hz), 3.93 (1 H, d, *J* 3.6 Hz), 3.83 (1 H, dd, *J* 3.6, 2.2 Hz), 2.50-2.44 (1 H, m), 2.08 (3 H, d, *J* 1.1 Hz), 1.85 (3 H, d, *J* 1.1 Hz), 1.40-1.21 (6 H, m), 0.99 (3 H, d, *J* 6.6 Hz), 0.89 (3 H, t, *J* 7.1 Hz); δ_C ($CDCl_3$, 125 MHz) 191.0, 188.4, 168.4, 144.0, 141.7, 139.0, 129.8, 127.7, 115.0, 53.8, 52.5, 36.9, 32.9, 29.7, 22.8, 20.6, 16.4, 14.0, 13.9; ν_{max} (film) 3382, 2958, 2925, 2869, 1679, 1608, 1504, 1317, 1213, 1174, 1081 cm^{-1}; *m/z* (CI) 349 (MNH_4^+, 15%), 332 (MH^+, 100) [Found: MH^+, 332.18571. $C_{19}H_{26}NO_4$ requires 332.18618 (1.4 ppm error)]; $[\alpha]_D$ -149.8 (*c* 1.5, $CHCl_3$).

Quinone 8b as a yellow oil (62% over 3 steps), R_f 0.27 (EtOAc-PE, 1:4); δ_H ($CDCl_3$, 500 MHz) 8.25 (1 H, br s), 7.56 (1 H, d, *J* 2.5 Hz), 6.26 (1 H, d, *J* 10.0 Hz), 3.93 (1 H, d, *J* 3.5 Hz), 3.83 (1 H, dd, *J* 3.5, 2.5 Hz), 2.55-2.44 (1 H, m), 1.92 (3 H, s), 1.48-1.17 (6 H, m), 1.02 (3 H, d, *J* 6.5 Hz), 0.87 (3 H, t, *J* 7 Hz); δ_C ($CDCl_3$, 125 MHz) 191.0, 188.4, 167.5, 146.2, 138.9, 129.1, 114.9, 53.8, 52.4, 36.4, 33.4, 29.6, 22.6, 19.9, 13.9, 12.4; ν_{max} (film) 3385, 2958, 2926, 2856, 1680, 1608, 1502, 1456, 1315, 1213, 1174, 1078, 1011 cm^{-1}; UV (MeOH) 313 (9900), 237 (11241); *m/z* (EI) 291 (M^+, 1%) [Found: M^+, 291.14771. $C_{16}H_{21}NO_4$ requires 291.14706 (2.2 ppm error)]; $[\alpha]_D$ -18.4 (*c* 1.1, $CHCl_3$) {Lit.[22] $[\alpha]_D$ +16.0 (*c* 0.2, $CHCl_3$)}.

Quinone 8c as a pale yellow oil (54% over 3 steps), R_f 0.40 (EtOAc-hexanes, 3-7); δ_H ($CDCl_3$, 500 MHz) 7.89 (1 H, br s), 7.63 (1 H, d, *J* 2.5 Hz), 7.37 (1 H, dd, *J* 15.5, 1.0 Hz), 5.87 (1 H, d, *J* 15.5 Hz), 5.79 (1 H, br d, *J* 10.0 Hz), 3.93 (1 H, d, *J* 3.5 Hz), 3.84 (1 H, dd, *J* 3.5, 2.5 Hz), 2.56-2.52 (1 H, m), 1.81 (3 H, d, *J* 1.0 Hz), 1.40-1.18 (6 H, m), 1.00 (3 H, d, *J* 7.0 Hz), 0.86 (3 H, t, *J* 7.0 Hz); δ_C ($CDCl_3$, 125 MHz) 191.0, 188.2, 165.2, 151.0, 150.5, 139.0, 130.9, 116.3, 115.1, 53.8, 52.4, 36.8, 33.4, 29.6, 22.7, 20.3, 14.0, 12.9; ν_{max} (film) 3319, 2960, 2925, 2856, 1691, 1668, 1604, 1504, 1317, 1215, 1176, 1144, 1014 cm^{-1}; UV (MeOH) 330 (21278), 271 (21221); *m/z* (CI) 335 (MNH_4^+, 95%), 318 (MH^+, 100) [Found: MNH_4^+, 318.17053. $C_{18}H_{24}NO_4$ requires 318.17053 (0 ppm error)]; $[\alpha]_D$ +8.5 (*c* 0.4, $CHCl_3$) {Lit.[22] $[\alpha]_D$ -14.0 (*c* 0.2, $CHCl_3$)}.

2-[(2'*E*, 4'*E*, 6'*S*)-2,4,6-Trimethyldeca-2,4-dienamido]-5,6-epoxy-4-hydroxy-4-(*E*-2''-tributylstannylethenyl)cyclohex-2-en-1-one 19

To freshly distilled *E*-1,2-bis(tributylstannyl)ethene[23] (200 mg, 0.33 mmol) in THF (2 mL) under argon at -78°C was added butyllithium (2.5 *M* solution in THF, 100 µL). The solution was kept at -78°C for 15 min, and then stirred at 0°C for 1 h. After dilution by THF (2 mL), the solution was cooled to -78°C and quinone **8a**(*S*) (40 mg, 0.12 mmol) in THF (2 mL) was slowly added over 10 min. The mixture was stirred at -78°C for an additional 30 min and quenched satd. aq.NH_4Cl (5 mL). The mixture was extracted EtOAc (3 x 5 mL), the combined organic layers dried over $MgSO_4$, and the solvent removed *in vacuo*. The product was isolated by column chromatography (PE then PE-EtOAc, 9-1), followed by preparative TLC (PE-EtOAc, 4:1) to give the title compound **19** (19.5 mg, 25%) as a colourless oil, R_f 0.22 (PE-EtOAc, 9:1); δ_H ($CDCl_3$, 500 MHz) 7.99 (1 H, br s), 7.38 (1 H, d, *J* 2.5 Hz), 6.79 (1 H, s), 6.49 (1 H, d, *J* 19.5 Hz), 5.99 (1 H, d, *J* 19.5 Hz), 5.33 (1 H, d, *J* 9.5 Hz), 3.67 (1 H, dd, *J* 3.5, 2.5 Hz), 3.65 (1 H, d, *J* 3.5 Hz), 2.60 (1 H, br s), 2.50-2.42 (1 H, m), 2.06 (3 H, s), 1.82 (3 H, s), 1.60-1.20 (24 H, m), 0.99 (3 H, d, *J* 6.5 Hz), 0.96-0.85 (12 H, m); δ_C ($CDCl_3$, 125 MHz) 189.4, 168.6, 145.5, 142.4, 139.9, 133.2, 129.9, 128.3, 127.9, 127.4, 72.9, 57.7, 52.9, 37.0, 32.8, 29.8, 29.0, 27.2, 22.8, 20.7, 16.5, 14.1, 14.0, 13.6, 9.6; ν_{max} (film) 3800, 2956, 2926, 2870, 2854, 1670, 1516, 1456, 1363, 1259, 1076, 1014 cm^{-1}; *m/z* (CI) 667 (MNH_4^+, 5%), 650 (MH^+, 35), 632 (M - OH, 20) [Found: MH^+, 648.32530. $C_{33}H_{56}NO_4{}^{118}Sn$ requires 648.32254 (4 ppm error)]; $[\alpha]_D$ +79.5 (*c* 0.85, $CHCl_3$).

(+)-Manumycin A 20

The catalyst bis(triphenylphosphine)palladium(II) chloride (0.5 mg, 0.7 µmol) in THF (1 mL) was treated with DibalH (1.0 *M* solution in THF, 30 µL) at rt under nitrogen and the mixture was stirred for 15 min. To 50 µL of this solution was added a solution of the stannane **19** (10 mg, 0.015 mmol) in degassed DMF (200 µL) followed by the bromodiene **7**[15b] (5 mg, 0.018 mmol) in degassed DMF (200 µL) under nitrogen at rt. The mixture was stirred 24 h at rt, diluted with EtOAc, washed 3 times with water, and dried over $MgSO_4$. Filtration and evaporation of the solvent *in vacuo* gave a yellow residue. The compound was purified by preparative TLC (DCM-MeOH, 95:5) to afford the title compound **20** (6 mg, 71%) as a yellow solid, m.p. 134-136°C; R_f 0.48 ($CHCl_3$-MeOH, 9:1); δ_H ($CDCl_3$, 500 MHz) 13.58 (1 H, s, OH_b), 7.98 (1 H, br s, NH_b), 7.50 (1 H, br s, NH_a), 7.39 (1 H, d, *J* 2.5 Hz, H-3), 7.33 (1 H, dd, *J* 15, 11.5 Hz, H-11), 6.79 (1 H, br s, H-3'), 6.65-6.50 (2 H, m, H-8 & H-9), 6.43 (1 H, dd, *J* 14, 11.5 Hz, H-10), 6.06 (1 H, d, *J* 15 Hz, H-12), 5.88 (1 H, d, *J* 14.5 Hz, H-7), 5.34 (1 H, br d, *J* 9.5 Hz, H-5'), 3.72 (1 H, dd, *J* 4.0, 2.5 Hz, H-5), 3.67 (1 H, d, *J* 4.0 Hz, H-6), 3.24 (1 H, br s, OH_a), 2.68-2.52 (2 H, m, H-4'' and H-5''), 2.51-2.42 (1 H, m, H-6'), 2.05 (3 H, d, *J* 1.5 Hz, Me-11'), 1.82 (3 H, d, *J* 1.5 Hz, Me-12'), 1.43-1.13 (6 H, m, 3 x CH_2 (7'-9')), 0.98 (3 H, d, *J* 6.4 Hz, Me-13'), 0.89 (3 H, t, *J* 7.0 Hz, Me-10'); δ_C ($CDCl_3$, 125 MHz) 197.4 (C-1''), 188.9 (C-1), 174.0 (C-3''), 168.8 (C-1'), 165.4 (C-13), 143.5 (C-11), 142.7 (C-5'), 140.2 (C-3'), 139.6 (C-9), 136.3 (C-7), 131.7 (C-10), 131.5 (C-8), 129.9 (C-4'), 128.2 (C-2'), 128.1 (C-2), 126.2 (C-3), 121.5 (C-12), 115.0 (C-2''), 71.2 (C-4), 57.4 (C-5), 52.9 (C-6), 37.0 (C-7'), 32.9 (C-6'), 32.1 (C-5''), 29.8 (C-8'), 25.6 (C-4''), 22.8 (C-9'), 20.7 (C-13'), 16.5 (C-12'), 14.1 (C-10'), 14.0 (C-11'); ν_{max} ($CDCl_3$) 3396, 3255, 2956, 2926, 2870, 1668, 1603, 1543, 1514, 1365, 1321, 1234, 1005 cm^{-1}; UV (MeOH) 314 (23800), 278 (29500), 263 (30300); *m/z* (FAB): 551 (MH^+, 20%), 533 (M-OH, 4), 193 (100) [Found: MH^+, 551.27599. $C_{31}H_{39}N_2O_7$ requires 551.27573 (0.5 ppm error]; $[\alpha]_D$ +193 (*c* 0.1, $CHCl_3$)

{Lit.[3] $[\alpha]_D$ (for enantiomer) -185 (*c* 0.4, $CHCl_3$)}. This data is entirely consistent to that published for the enantiomer.[3]

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