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Toward the synthesis of tetrodecamycin: asymmetric synthesis of a direct precursor of the C6–C18 *trans*-decalin portion

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Abstract—We report the asymmetric synthesis of a direct precursor of the C6–C18 *trans*-decalin portion of tetrodecamycin utilising an asymmetric intramolecular Diels–Alder (IMDA) reaction as the key step.

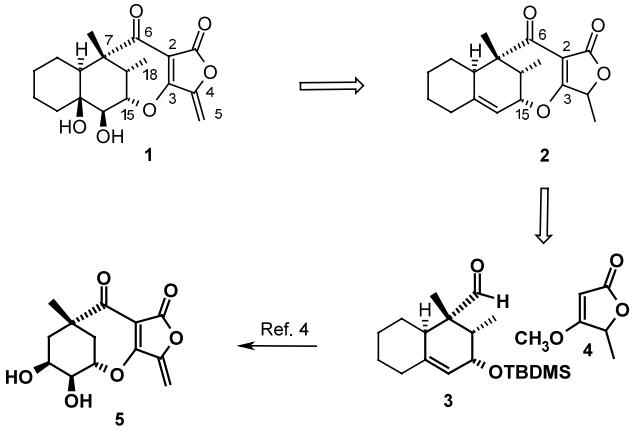
Tetrodecamycin **1** is a novel α-(γ-hydroxyacyl) tetronic acid based polyketide antibiotic isolated from the culture broth of *Streptomyces nashvillensis* in 1994 by Takeuchi and co-workers.[1] It shows distinct activity against Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) as well as *Bacillus anthracis*. The unique ring skeleton and absolute configuration of compound **1** were fully elucidated by 2D NMR and X-ray crystallography.[2] However, no total synthesis of this interesting antibiotic has been reported so far.

Our approach to tetrodecamycin **1** is based on key intermediate **2**, which is envisioned to arise from aldehyde **3** and 4-methoxy-5-methyl-5*H*-furan-2-one (**4**),[3] involving disconnections of the tetracyclic structure at the C2–C6 and the C3–O or C15–O bonds (Scheme 1). In a recent publication we have disclosed an efficient approach to the core structure **5** of tetrodecamycin, starting from **4** and an appropriate aldehyde, which represents a close model of aldehyde **3** (bold type in Scheme 1).[4]

In this letter we report the asymmetric synthesis of key building block **3**, which contains four of the six stereogenic centres inherent in the target molecule **1**.

Our strategy is founded on: (a) the asymmetric intramolecular Diels–Alder (IMDA) reaction of trienimide **6**, where the simultaneous generation of the four stereogenic centres at C1, C2, C4a and C8a of the resulting octahydronaphthalene ring skeleton was to be directed by Evan's chiral 4-benzyl-2-oxazolidinone auxiliary,[5] and (b) the stereoselective transformation of acid **7** into lactone **8**, suitably functionalised for conversion into target molecule **3** (Scheme 2).

The synthesis of cyclisation precursor **6** was begun by Li_2CuCl_4-catalysed cross coupling[6] between the Grignard reagent **10**, prepared from 2-(3-bromopropyl)-1,3-dioxolane,[7] and commercially available (2*E*,4*E*)-2,4-hexadien-1-yl acetate (**9**) to yield (6*E*,8*E*)-deca-6,8-dienal (**12**)[8] after hydrolysis of the corresponding acetal **11** with aqueous acetic acid (61% from **9**) (Scheme 3).[9]



Scheme 1.

Keywords: tetrodecamycin; antibiotics; asymmetric synthesis; Diels–Alder reactions; lactonisation.

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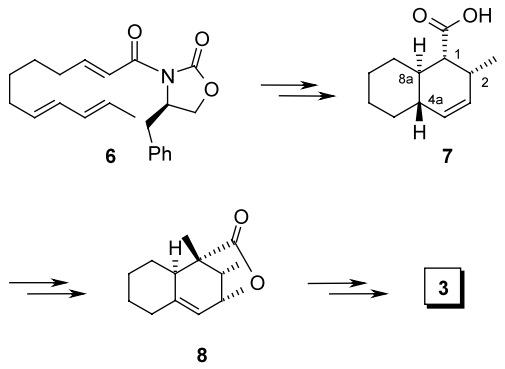
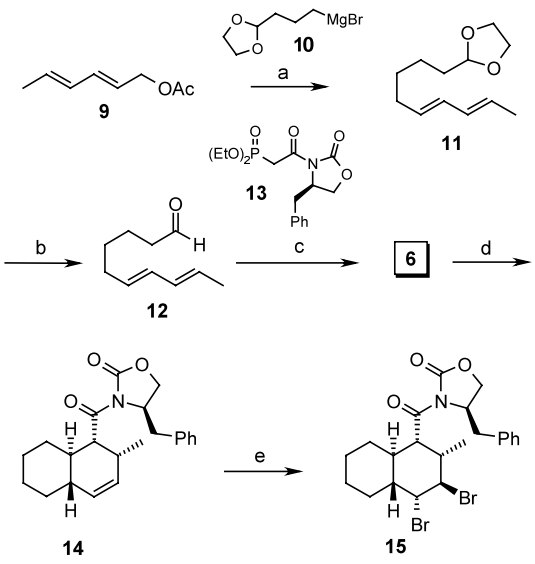


Scheme 2.



Scheme 3. *Reagents and conditions*: (a) Li_2CuCl_4 (cat.), THF, –20°C (69%); (b) AcOH, H_2O, THF, 80°C (88%); (c) LiCl, *i*-Pr_2NEt, CH_3CN, rt (91%); (d) Me_2AlCl (1.4 equiv.), CH_2Cl_2, –30°C (92%); (e) Br_2, CH_2Cl_2, 0°C (66%).

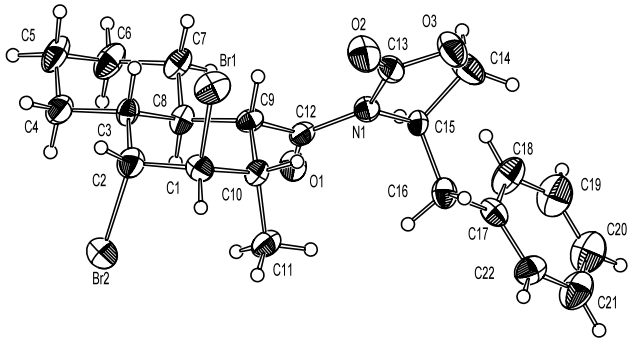
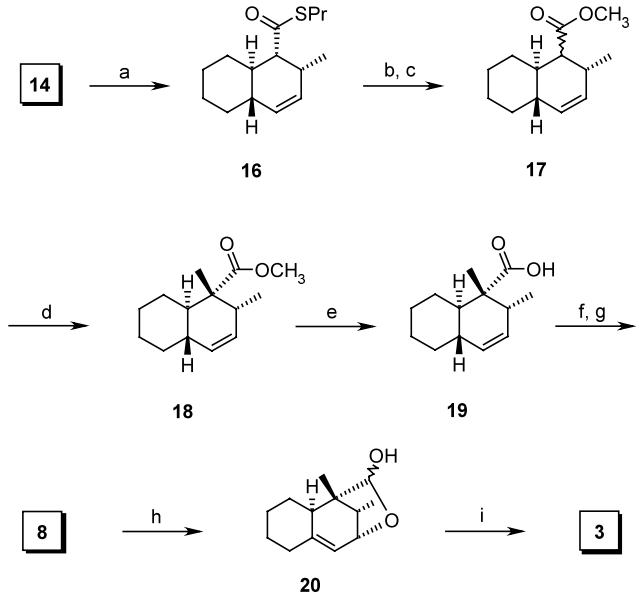


Figure 1. ORTEP plot of **15**.

Modified Horner–Wadsworth–Emmons reaction[10] of aldehyde **12** with the chiral phosphonate **13**[11] selectively led to the triene **6** in 91% yield ($E{:}Z \geq 95{:}5$). With the chiral triene **6** in hand, asymmetric intramolecular Diels–Alder (IMDA) reaction was performed following the reaction conditions reported by Evans.[5] Thus treatment of a dilute solution of the triene **6** in dichloromethane with dimethylaluminium chloride (1.4 equiv.) at –30°C for 21 h provided the desired cycloadduct **14** with high diastereoselectivity [d.s. (*endo*) ≥ 98:2; Σ*endo*:Σ*exo* ≥ 50:1] and in excellent yield (92%). The relative configuration of C1, C2, C4a and C8a in **14**[12] was determined on the basis of the ^1H–^1H *J*-coupling values and NOE studies. The absolute configuration assigned for **14** was confirmed by X-ray diffraction analysis of the dibromo derivative **15**[13] (Fig. 1), which was obtained in 66% yield from **14** on treatment with bromine (CH_2Cl_2, 0°C).

To introduce the missing C1 methyl group by alkylation of an appropriate enolate, the *N*-acyloxazolidinone **14** was transformed into the methyl ester **17** (Scheme 4). Since removal of the chiral auxiliary by hydrolysis with lithium hydroperoxide (2.0 equiv. LiOH, 8.0 equiv. H_2O_2, THF/H_2O, 0°C to rt)[14] failed, due to competing endocyclic cleavage of the *N*-acyloxazolidinone,[15] the cycloadduct **14** was first converted into the thioester **16** by Damon's lithio mercaptide method[16] (96% yield; 92% recovery of the chiral auxiliary). Subsequent hydrolysis of the thioester **16** led to the acid **7**, which was converted to the methyl ester **17** in 90% overall yield (~4:1 mixture of diastereomers due to partial epimerisation in the course of alkaline hydrolysis).

Stereoselective methylation at C1 was achieved by converting the methyl ester **17** first into the corresponding lithio enolate (1.25 equiv. LDA, THF, –78°C to rt) and



Scheme 4. *Reagents and conditions*: (a) PrSLi, PrSH, THF, 0°C (96%); (b) 2 M aq NaOH, MeOH, 120°C; (c) trimethyloxonium tetrafluoroborate, *i*-Pr_2NEt, CH_2Cl_2, rt (90% from **16**); (d) (i) LDA, THF, –78°C to rt; (ii) CH_3I, –90°C to rt (84%); (e) 3 M NaOH aq., MeOH, 125°C (91%); (f) PhSeCl, CH_2Cl_2, –78°C to rt; (g) MMPP/SiO_2, CH_2Cl_2, rt (90% from **19**); (h) DIBAL, CH_2Cl_2, –78°C (74%); (i) TBDMSOTf, *i*-Pr_2NEt, CH_2Cl_2, 0°C (65%).

then by reacting it with methyl iodide (–90°C to rt) to form **18** as the major isomer of a separable 88:12 mixture of diastereomers in 84% yield. The relative configuration of **18** was assigned on the basis of NOE experiments. Thus irradiation of the CH_3 group at C1 gave rise to a significant NO effect for 2-H.

Hydrolysis of the methyl ester **18** had to be run under forced conditions (3 M NaOH aq., MeOH, 125°C, 10 h) to obtain acid **19** in good yield (91%). The stereospecific transformation of the γ,δ-unsaturated acid **19** into lactone **8** was achieved by phenylselenolactonisation[17] (PhSeCl, CH_2Cl_2, −78°C to rt, 7d) and subsequent oxidative removal (MMPP/SiO_2, CH_2Cl_2, rt) of the phenylselenanyl substituent to establish the crucial C4–C4a double bond. Thus the unsaturated lactone **8** was obtained in high overall yield (90%). Finally conversion of **8** into TBDMS-protected γ-hydroxy aldehyde **3** was accomplished by a two-step protocol. First lactone **8** was reduced to the corresponding lactol **20** (3.0 equiv. DIBAL, CH_2Cl_2, −90°C) in 79% yield, which provided the building block **3**[18] in 65% yield on treatment with TBDMSOTf (*i*-Pr_2NEt, CH_2Cl_2, 0°C).[19]

In conclusion, we have developed an efficient synthetic pathway to a direct precursor of the C6–C18 *trans*-decalin portion of tetrodecamycin (**1**). Further synthetic studies toward **1** starting from key building block **3** are now in progress and will be reported in due course.

Acknowledgements

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12. **14**: $[\alpha]_D^{20}$ −185° (*c* 0.96, CH_2Cl_2). IR (KBr): 3012, 2923, 1780, 1696, 1508, 1386, 1196 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) $\delta=0.87$ (m, 1H, 8-H_{ax}), 0.96 (d, 3H, $J=7.2$ Hz, CH_3), 1.12 (m, 1H, 5-H_{ax}), 1.25–1.45 (m, 2H, 6-H_{ax} and 7-H_{ax}), 1.60 (m, 1H, 8a-H), 1.73–1.81 (m, 4H, 4a-H, 5-H_{eq}, 6-H_{eq} and 7-H_{eq}), 1.91 (m, 1H, 8-H_{eq}), 2.63 (dd, 1H, $J=10.6$, 13.1 Hz, CH_2Ph), 2.81 (m, 1H, 2-H), 3.42 (dd, 1H, $J=3.3$, 13.1 Hz, CH_2Ph), 3.82 (dd, 1H, $J=5.9$, 11.3 Hz, 1-H), 4.12–4.19 (m, 2H, OCH_2), 4.72 (ddd, 1H, $J=3.4$, 7.0, 13.9 Hz, NCH), 5.41 (br d, 1H, $J=9.9$ Hz, 4-H), 5.58 (ddd, 1H, $J=2.6$, 4.6, 9.9 Hz, 3-H), 7.23–7.31 (m, 3H, H_{arom}), 7.32–7.37 (m, 2H, H_{arom}). ^{13}C NMR (500 MHz, $CDCl_3$) $\delta=17.77$ (CH_3), 26.59, 26.70 (C-6 and C-7), 30.09 (C-8), 30.92 (C-2), 33.17 (C-5), 36.59 (C-8a), 38.29 (CH_2Ph), 41.89 (C-4a), 47.67 (C-1), 55.36 (NCH), 66.02 (OCH_2), 127.31, 128.99, 129.34 (C_6H_5), 130.70, 130.83 (C-3 and C-4), 135.52 (C_6H_5), 153.05 (NC=OO), 173.61 (NC=O). MS (CI, CH_5^+): *m*/*z* (%)=354 (100) [M+H^+], 177 (60). Anal. calcd for $C_{22}H_{27}NO_3$ (353.5): C, 74.76; H, 7.70; N, 3.96. Found: C, 74.53; H, 7.73; N, 3.87%.
13. Crystallographic data (excluding structure factors) for structure **15** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC199999. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail:deposit@ccdc.cam.ac.uk].
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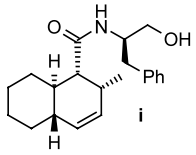
15. The carboxylic acid **7** and the chiral auxiliary were obtained only in low yield (12 and 10%, respectively) in addition to the cleavage product **i**, which was formed in 85% yield.



i

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18. **3**: Colorless oil; $[\alpha]_D^{20}=-124°$ (*c* 1.2, CH_2Cl_2). IR (film): 2930, 1722, 1675, 1462, 1256 cm^{-1}. ^1H NMR (500 MHz; CD_2Cl_2) $\delta=0.04$ (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.86 [s, 9H, $C(CH_3)_3$], 0.89 (br d, 3H, $J\sim6.5$ Hz, $CHCH_3$), 0.97 (s, 3H, CH_3), 1.09 (m, 1H, 8-H_{ax}), 1.21 (m, 1H, 6-H_{ax}), 1.44 (m, 1H, 7-H_{ax}), 1.68 (m, 1H, 8-H_{eq}), 1.77–1.86 (m, 2H, 6-H_{eq} and 7-H_{eq}), 1.92 (ddd, 1H, $J=4.1$, 7.1, 14.2 Hz, 2-H), 2.03 (m, 1H, 5-H_{ax}), 2.22 (dquin, 1H, $J=2.1$, 12.8 Hz, 5-H_{eq}), 2.27 (m, 1H, 8a-H),

4.13 (br s, 1H, 3-H), 5.30 (br s, 1H, 4-H), 9.58 (s, 1H, CHO). ^{13}C NMR (500 MHz, CD_2Cl_2) $\delta = -5.23$ ($SiCH_3$), −4.57 ($SiCH_3$), 10.10 ($CHCH_3$), 16.90 (CH_3), 18.01 [$C(CH_3)_3$], 25.57 [$C(CH_3)_3$], 26.69 (C-7), 28.49 (C-6), 29.75 (C-8), 36.01 (C-5), 39.13 (C-2),), 47.30 (C-8a), 68.25 (C-1), 68.37 (C-3), 121.15 (C=CH), 135.66 (C=CH), 204.47 (CHO). MS (CI, CH_5^+): m/z (%) = 323 (7) [M+H$^+$], 207 (100). HRMS: m/z calcd for $C_{19}H_{34}O_2Si$ (M^+): 322.2328. Found: 322.2332.

19. The remaining material was the corresponding TBDMS-protected lactol, which after chromatographic separation and deprotection (HF, acetonitrile, 0°C) could be recycled.