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Total Asymmetric Synthesis of *Seco*-Acids of 9,12-Anhydroerythronolide Aglycons

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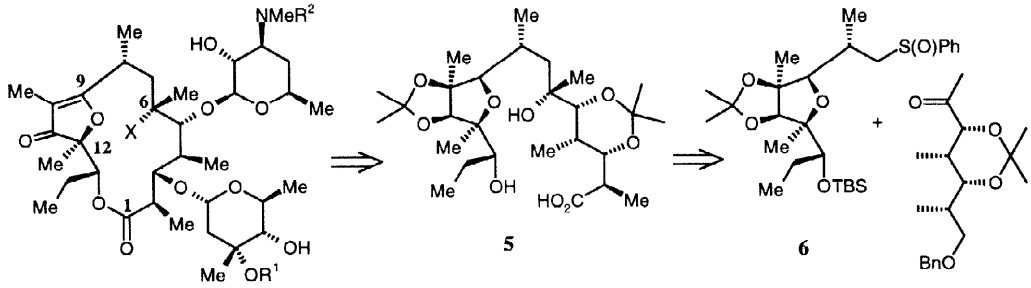
Abstract:

The Diels-Alder adduct of 2,4-dimethylfuran to 1-cyanovinyl (1'*S*)-camphanate was converted into (2*R*,3*R*,4*S*,5*S*,6*R*,7*R*)-3,6-epoxy-4,5-isopropylidenedioxy-2,4,6-trimethyl-7-[(*tert*-butyl)-dimethylsilyloxy]non-1-yl phenyl sulfoxides (**6**), the condensation of which with (3*R*,4*S*,5*R*,6*S*)-7-benzyloxy-3,5-isopropylidenedioxy-4,6-dimethylheptan-2-one (**7**) led to the partially-protected *seco*-acid of the 9,12-anhydroerythronolide aglycon (**5**).

Keywords: antibiotics; bicyclic heterocyclic compounds; furans; polyketides.

The urgent need for new antibiotics [1] has stimulated the search for new microorganism metabolites and of chemically-modified known antibiotics. Sporeamicin A (**1**), produced by *Saccharopolyspora* sp. L53-18A was isolated and characterized in 1992 by Morishita *et al.* [2]. It is strongly active against Gram-positive bacteria [3]. Structurally, **1** is an oxidized form of erythromycin with a 9,12-anhydro moiety. Sporeamicin B (**2**) [4] and C (**3**) [5] have also been isolated. In 1996, 6-deoxysporeamicin A (**4**) [6] was derived from 6-deoxyerythromycin A. The antibacterial spectrum of **4** is similar to that of erythromycin but is has greater potency against susceptible streptococci [6]. Other anhydro-derivatives of erythromycin A such as the neotilides (8,9-anhydro-6,9-hemiacetals) have been described and were shown to stimulate gastrointestinal motility [7].



1 R^1 = Me, R^2 = Me, X = OH **3** R^1 = Me, R^2 = H, X = OH
2 R^1 = H, R^2 = Me, X = OH **4** R^1 = Me, R^2 = Me, X = H

There have been numerous investigations into the total synthesis of erythromycins [8]. None of them, however, has generated analogues containing a tetrahydrofuran ring as in **1-4**. We have shown that the readily available Diels-Alder adducts of 2,4-dimethylfuran to 1-cyanovinyl camphanates ((+)-**8**, (+)-**9**, "*naked sugars of the second generation*") [9] can be converted into enantiomerically-pure polypropionate fragments of high complexity [10].

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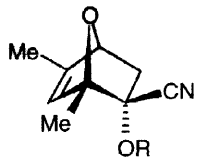
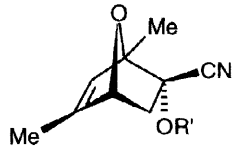
In this report, we demonstrate that (-)-**8** can be converted into the tetrahydrofuran derivative **6**, the condensation of which the known polypropionate fragment **7** leads to *seco*-acids of 9,12-anhydroerythronolides, potential precursors of the sporeamicins **1-4**.

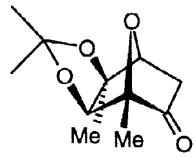
R = (1*S*)-camphanoyl
R' = (1*R*)-camphanoyl



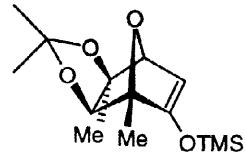
(-)-**8**



(+)-**9**

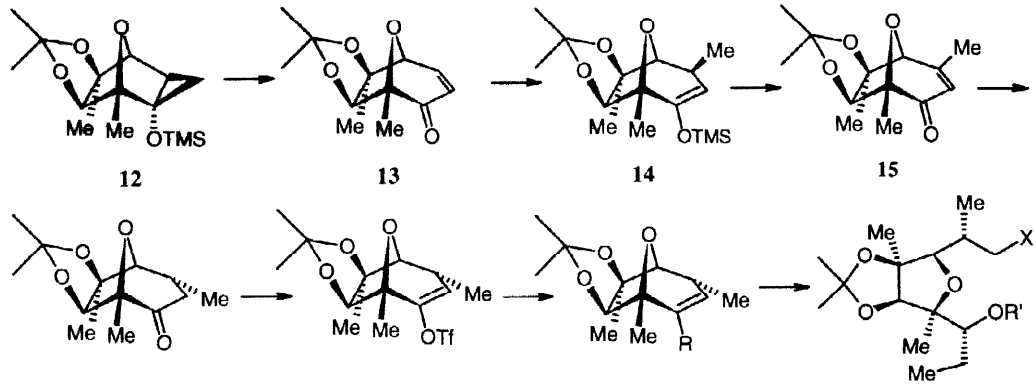


(-)-**10**



(+)-**11**

Double hydroxylation of (-)-**8**, followed by protection of the diol as its acetonide and saponification of the camphanate (recovery of the chiral auxiliary, (1*S*)-camphanic acid) [10b] provided ketone (-)-**10** (78 %, 3 steps). Treatment of (-)-**10** with 1 equivalent of $(i\text{-}Pr)_2NLi$ (-78 °C, 75 min, THF) and then with Me_3SiCl (-78 °C to 20 °C, 3.5 h) [11] gave enoxysilane **11** (98 %). Cyclopropanation of **11** with Et_2Zn/ICH_2Cl ($ClCH_2CH_2Cl$, 0 °C, 2.5 h) [12] furnished **12** which was oxidized with $FeCl_3$/pyridine [13] (0-40 °C, 3 h) to give the enone **13** (81 %, 2 steps). Michael addition of methylcuprate (CuBr.DMS/MeLi, Et_2O, -78 °C) followed by quenching of the enolate with Me_3SiCl (-78 °C to 20 °C, 15 h) [14] provided **14** (98 %). Oxidation of **14** (O_2/DMSO/0.09 equiv. $Pd(OAc)_2$, 50 °C, 2 days) [15] led to enone **15**, the hydrogenation of which, with $Ph_2SiH_2/ZnCl_2$/0.1 equiv. of $Pd(OAc)_2(PPh_3)_2$ and PPh_3 ($CHCl_3$, 70 °C, 4 h) [16] gave the ketone **16** with a 4-*endo* methyl substituent, as confirmed by the ^{1}H-NMR spectrum ($^3J_{H4,H5}$) [1]. Conversion of **16** into its enol triflate [$(i\text{-}Pr)_2NLi$, THF, -78 °C, then 2-[*N,N'-bis*(trifluoromethylsulfonyl)amino]-5-chloropyridine] [17] followed by Stille coupling with tributylvinylstannane (LiCl, 0.02 equiv. of $Pd(PPh_3)_4$, THF, 65 °C, 24 h) [18] provided the diene **18** (96 %). Selective reduction of the vinyl moiety into an ethyl group was achieved on treating **18** with a large excess of $H_2NNH_2.H_2O$ and H_2O_2 (35 %) in the presence of $Cu(OAc)_2$ as catalyst (MeOH, -15 °C to -5 °C, 2.5 h) [19]. This gave **19** (74 %), the ozonolysis of which (O_3/CH_2Cl_2/MeOH, -78 °C; then Me_2S) and reduction with $NaBH_4$ (-78 °C to 20 °C, 2.5 h) furnished a 3:1 mixture of diols, the major diastereoisomer having the configuration shown in **20**, as established by X-ray crystallography [2].



12 **13** **14** **15**

16 **17**

18 R = $CH{=}CH_2$ **20** X = OH, R' = H **22** X = SPh, R' = TBS
19 R = Et **21** X = SPh, R' = H **6** X = S(O)Ph, R' = TBS

Selective displacement of the primary alcohol moiety of **20** by phenylsulfide was possible on treatment with PhSSPh and $(n\text{-}oct)_3P$ (MeCN), 20 °C, 24 h). This led to **21** (95 %, 3:1 mixture of diastereomeric alcohols, separated by flash

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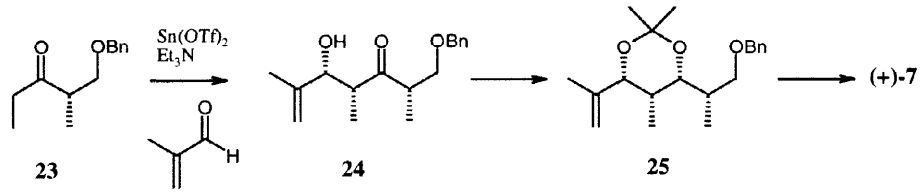
[1] Data for (-)-**16**: Colourless oil. $[\alpha]^{25}_D$ = -35, (c= 1.9, $CHCl_3$). IR (Film): 2984, 2936, 1725, 1379, 1217, 1084, 821. ^{1}H NMR (400 MHz, $CDCl_3$): 4.09 (*dd*, ^3J=3.6, ^4J=2.2, H-C(5)); 4.08 (*s*, H-C(7)); 2.61 (*ddd*, ^4J=2.2, ^3J=6.3, ^2J=19.2, H-C(3)); 2.56 (*ddd*, ^3J=3.6, 6.3, 14.6, H-C(4)); 2.06 (*dd*, ^2J=19.2, ^3J=14.6, H-C(3)); 1.66, 1.53, 1.48, 1.33 (4 x *s*, 4 x Me); 1.13 (*d* ^3J=7.2, Me-C(4)). ^{13}C NMR (100 MHz, $CDCl_3$): 206.1, 113.6, 92.4, 89.9, 89.7, 86.6, 42.3, 35.6, 29.4, 27.9, 23.0, 13.8. CI-MS (NH_3): 240 (3, M^+), 225 (77, $[M\text{-}Me]^+$), 207 (12), 189 (19), 164 (8), 135 (19), 111 (70), 97 (82), 85 (100). Anal. calc. for $C_{13}H_{20}O_4$: C 64.98, H 8.39. Found: C 64.94, H 8.46.

[2] Schenk K. Institut de Cristallographie, Université de Lausanne. Details will be given in a forthcoming full-paper.

chromatography at this stage) the major isomer being protected as a silyl ether with (*t*-Bu)Me_2SiOTf/2,6-lutidine (CH_2Cl_2, 0 °C, 2 h), giving **22** (89 %) [3]. Oxidation of **22** with $NaIO_4$ in 17:1 MeOH/H_2O (20 °C, 48 h) provided **6** as a 1.5:1 mixture of two diastereoisomeric sulfoxides.

The known methylketone **7** [20] was derived from Paterson's chiron **23** [21]. Tin-aldol reaction with an excess of methacrolein ($Sn(OTf)_2$, Et_3N, CH_2Cl_2, -78 °C, 1 h) gave **24** (81 %, *syn/anti* selectivity: 9:1). Treatment of **24** with Bu_2BOMe, then with $LiBH_4$ (THF) [21] furnished a diol which was protected ($Me_2C(OMe)_2$, PPTS, CH_2Cl_2, 18 h) as its acetonide (**25**) (89 %, 2 steps). Ozonolysis of **25** (O_3, CH_2Cl_2, MeOH, $NaHCO_3$, -78 °C, then Me_2S, 0 °C to 20 °C, 10 h) provided (+)-**7** (98 %) [4].



The coupling of synthons **6** and (+)-**7** was realised by lithiation of **6** with $LiNEt_2$ (THF, -60 °C 15 min) and then addition of a THF solution of (+)-**7** (-60 °C to –25 °C, 35 min). **6** was separated from the crude mixture of adducts by flash chromatography and **26** was then desulfurized by W2-Raney nickel (Et_2O/EtOH, 20 °C, 45 min) and debenzylated (W2-Raney nickel, 1 atm H_2, EtOH, 15 h) to give a separable 5:1 mixture of diols **27a** [5] and **27b** (65 %).
Swern oxidation of **27a** gave aldehyde **28** which was oxidized with $NaClO_2$/NaH_2PO_4 (H_2O/*t*-BuOH, 2-methylbut-2-ene, 20 °C, 30 min) to the carboxylic acid **29**. Desilylation of **29** with 40 % aqueous HF (MeCN, 20 °C, 2 h) provided **5** (68 %) [6]. The configuration of the tertiary alcohol at C^6 in **5** was deduced from nOe measurements on **30**, a derivative of **27a** [formation of **30** by cleavage of the dioxane and the TBS ether (2 M aq. HCl, THF, 50 °C, 4 h) and then protection

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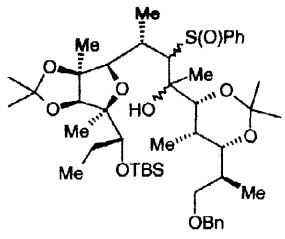
[3] Data for (-)-22: $[\alpha]^{25}_D$ = -20 (c= 1.88, $CHCl_3$). IR (Film): 2929, 1586, 1462, 1379, 1256, 826, 765, 738, 669. ^{1}H NMR (400 MHz, $CDCl_3$): 7.37 (*dd*, ^4J=1.5, ^3J=8.5, H-$_{ortho}$); 7.27 (*t*, ^3J=7.7, H-$_{meta}$); 7.15 (*dt*, ^4J=1.2, ^3J=7.3, H-$_{para}$); 4.23 (*s*, H-C(3)); 3.50 (*d*, ^3J=10.3, H-(C5)); 3.46 (*d*, ^3J=10.2, H-(C5)); 3.41 (*dd*, ^3J=2.7, ^2J=13.3, one of SCH_2); 3.38 (*dd*, ^3J=3.6, 6.9 *CH*OSi); 2.64 (*dd*, ^2J=13.3, ^3J=9.1, one of SCH_2); 1.85-1.75 (fused multiplets, one of $MeCH_2$ and MeC*H*); 1.54 (*s*, Me); 1.47 (*sept*, ^3J=7.2, one of $MeCH_2$); 1.35, 1.35, 1.17 (3 x *s*, 3 x Me); 1.07 (*d*, ^3J=6.5, *Me*CH); 1.01 (*t*, ^3J=7.5, *Me*CH_2); 0.89 (*s*, *t*-Bu); 0.12 and 0.10 (2 x *s*, 2 x *Me*Si). ^{13}C NMR (100 MHz, $CDCl_3$): 137.6, 128.7, 128.3, 125.2, 113.7, 90.0, 87.9, 84.6, 84.1. 78.4, 38.2, 33.0, 28.1, 26.0, 19.5, 18.3, 15.0, 14.6, 11.2, -3.8, -4.1. CI-MS (NH_3): 403 (100, M^+-$PhCH_2$); 345 (17); 271 (15); 229 (22); 157 (12); 91 (8). Anal. calc. for $C_{27}H_{46}O_4SSi$: C 65.54, H 9.37, S 6.48. Found: C 65.60, H 9.29, S 6.47.

[4] Data for (+)-7: Colourless needles, m.p. 40-41 °C. $[\alpha]^{25}_D$ = 30 (c=1, $CHCl_3$). IR (film) 3064, 3032, 2991, 2936, 2882, 1716, 1455, 1384, 1355, 1202, 1159, 1109, 1016, 985, 917, 868, 736, 699. ^{1}H NMR (400 MHz, $CDCl_3$): 7.37-7.27 (*m*, 5H, Ar); 4.49 (*br s*, $PhCH_2$); 4.26 (*d*, ^3J=2.6, H-C(3)); 3.72 (*dd*, ^3J=2.0, 9.6, H-C(5)); 3.34 (ABX system with δ_A=3.36, δ_B=3.32; $^2J_{AB}$=9.3, $^3J_{AX}$=5.3, $^3J_{BX}$=5.0, CH_2OBn); 2.16 (*s*, MeC=O); 2.04-2.01 (*m*, H-C(4)); 1.87-1.83 (*m*, H-C(6)); 1.49 (*s*, *Me*-(^{i}Pr)); 1.41 (*s*, *Me*-(^{i}Pr)); 1.06 (*d*, ^3J=6.6, Me-C(4)); 0.81 (*d*, ^3J=6.7, Me-C(6)). ^{13}C-NMR (100 MHz, $CDCl_3$): 209.7, 138.8, 128.2, 127.5, 99.3, 79.3, 75.1, 73.1, 71.1, 34.8, 32.2, 29.7, 27.0, 19.1, 14.5, 6.3. MS (CI-NH_3): 321 (4, M+1^+), 277 (10), 263 (4), 245 (13), 219 (3), 173 (3), 155 (9), 127 (7), 91 (100).

[5] Data for (+)-27a: Colourless oil, $[\alpha]^{25}_D$ = 3.7 (c=1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): 4.19 (*s*, H-(C11)); 4.07 (*br s*, OH); 3.65 (*dd*, ^3J=4.2, ^2J=10.7, one of CH_2OH)); 3.59 (*dd*, ^3J=2.1, 9.3, H-(C3)); 3.55 (*dd*, ^2J=5.4, ^3J=10.7, one of CH_2OH); 3.52 (*d*, ^3J=10.7, H-(C5)); 3.37 (*d*, ^3J=10.0, H-(C9)); 3.35 (*dd*, ^3J=2.9, 7.7, H-(COSi)); 1.86 (*dqd*, ^3J=2.8, 7.2, 10.0, H-(C8)); 1.84-1.76 (*m*, H-(C2), H-(C4), both of H-(C7)); 1.70 (*dqd*, ^3J=2.9, 7.7, ^2J=15.1, one of CH_2CHOSi); 1.65-1.54 (*m*, one of CH_2CHOSi); 1.52 (*s*, Me); 1.44, 1.40, 1.39, 1.34, 1.22, 1.14 (6 x *s* , 6 x Me); 1.04 (*d*, ^3J=6.8, *Me*-(C2)); 1.01 (*d*, ^3J=6.8, *Me*-(C4)); 0.96 (*d*, ^3J=7.2, *Me*-C(8)); 0.78 (*t*, ^3J=7.7, *Me*CH_2); 0.91 (*br s*, *t*-Bu); 0.11, 0.10 (2 x *s*, 2 x MeSi). ^{13}C-NMR (100 MHz, $CDCl_3$): 113.4, 99.1, 90.1, 87.6, 86.7, 84.7, 80.4, 78.4, 74.3, 72.7, 64.1, 45.7, 36.4, 31.2, 28.1, 27.6, 26.0, 25.0, 23.4, 19.3, 18.8, 14.1, 11.2, 7.1, -3.6, -4.2. MS (CI-NH_3): 617 (57, M+1^+), 559 (100, M^+-*t-Bu*), 523 (43), 483 (11), 429 (95), 367 (12), 297 (9), 255 (21), 225 (10), 173 (20) 73 (24).

[6] Data for (+)-5: $[\alpha]^{25}_D$ = 1.7 (c=0.5, $CHCl_3$). M.S. (CI-NH_3): 534 (2, M+NH_4^+), 516 (1, M^+), 472 (1, M+-CO_2), 441 (7), 294 (12), 276 (62), 259 (100), 248 (9), 243 (45), 227 (12), 215 (28), 204 (20), 157 (12), 99 (22).

of four of the five OH groups of the resulting pentol ($Me_2C(OMe)_2$, PPTS, CH_2Cl_2 20 °C, 2 days)] to give the *tris*-acetonide **30**. The configuration is in accord with results obtained by Stork [22] and Kochetkov [23].



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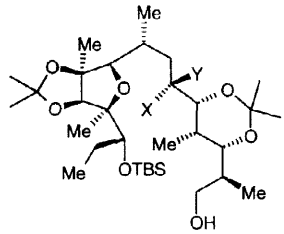
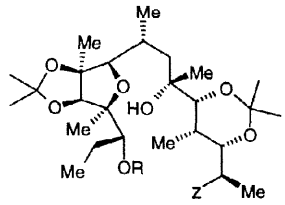
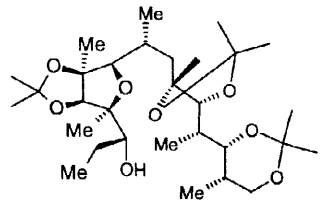


27a X = OH, Y = Me
27b X = Me, Y = OH



28 R = TBS, Z = CHO
29 R = TBS, Z = COOH
5 R = H, Z = COOH



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The present study demonstrates that "*naked sugars of the second generation*" can be converted into polypropionate fragments containing tetrahydrofuran rings, allowing the preparation of sporeamicin aglycon analogues. Work is underway in our laboratory to convert *seco*-acids such as **5** into the corresponding macrolides.

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