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Synthesis of (±)-dehydropentenomycin and analogues†

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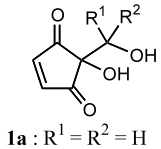
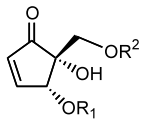
Abstract—(±)-Dehydropentenomycin and analogues were synthesized by utilizing the intramolecular acylation of α-sulfinyl carbanions, starting from alkyl 2,2-dimethyl-1,3-dioxolanecarboxylates.

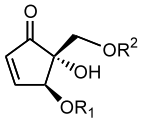
Dehydropentenomycin (antibiotic G-2201-C) (**1a**) isolated from *Streptomyces cattleya*[1] is one of the most simple cyclopentenoid antibiotics. Other members possessing a similar skeleton, pentenomycins I–III (**2**) and epipentenomycin I (**3**), were isolated from culture broths of *Streptomyces eurythermus*[2] and from carpophores of *Perziza* sp.,[3] respectively. Due to their interesting biological activities against Gram-positive and Gram-negative bacteria, this type of compound has received considerable attention. Although several synthetic approaches to pentenomycins I–III and their epimers both in racemic and enantiopure forms have appeared in the literature,[4a–j] only few publications are concerned with the syntheses of dehydropentenomycin.[4a,b] In connection with our recent reports on general approaches to highly functionalized cyclopentenones as well as the preparation of (±)-pentenomycin I (**2**, $R^1=R^2=H$) and its epimer[4g] based on the sequential intramolecular acylation of α-sulfinyl carbanions followed by sulfoxide elimination,[5] we wish to report herein a new synthetic route to (±)-dehydropentenomycin (**1a**) and its analogues (**1b–d**) starting from alkyl 2,2-dimethyl-1,3-dioxolanecarboxylates.



1a : $R^1 = R^2 = H$
(Dehydropentenomycin)
1b : $R^1 = R^2 = Me$
1c : $R^1 = H$, $R^2 = Et$
1d : $R^1 = H$, $R^2 = Pr^i$



2 (Pentenomycins)
I : $R^1 = R^2 = H$
II : $R^1 = H$, $R^2 = Ac$
III : $R^1 = Ac$, $R^2 = H$



3 (Epipentenomycins)
I : $R^1 = R^2 = H$
II : $R^1 = H$, $R^2 = Ac$
III : $R^1 = Ac$, $R^2 = H$

As summarized in Scheme 1, the key intermediates for the cyclisation, hydroxysulfoxides **6** could be easily prepared from esters **4**. Treatment of enolate anions of **4**,[6] generated by employing lithium diisopropylamide (LDA, 1 equiv.) in THF at −78°C for 2 h, with 3-phenylsulfanylpropanal (1.1 equiv.) provided hydroxysulfides **5** in moderate to good yields (60–75%) as mixtures of diastereomers. These mixtures were then subjected to oxidation with $NaIO_4$ (1.1 equiv.) in aqueous methanol at 0°C to room temperature overnight to afford the corresponding hydroxysulfoxides **6** as diastereomeric mixtures in 69–76% yields after chromatography. Cyclisation of the hydroxysulfoxides **6** to the expected α-phenylsulfinyl cyclopentanones **7** was readily accomplished by treatment with 3.2 equiv. of LDA in THF at −78°C for 2 h and at 0°C for a further 2 h. The formation of **7** could be envisaged to occur through an intramolecular acylation reaction of the initially formed α-sulfinyl carbanions derived from **6**. Sulfoxide elimination of the cyclized products **7** was effected by flash vacuum pyrolysis at 340°C (0.01–0.08 mmHg) or refluxing in dry toluene in the presence of anhyd. $CaCO_3$ for 10–12 h to give diastereomeric mixtures of 4-hydroxyspirocyclopentenones **8** in 50–87%

Keywords: dehydropentenomycin; sulfoxides; acylation; antibiotics; carbanions; cyclisation.

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† Dedicated to Professor Dieter Seebach on the occasion of his 65th birthday.

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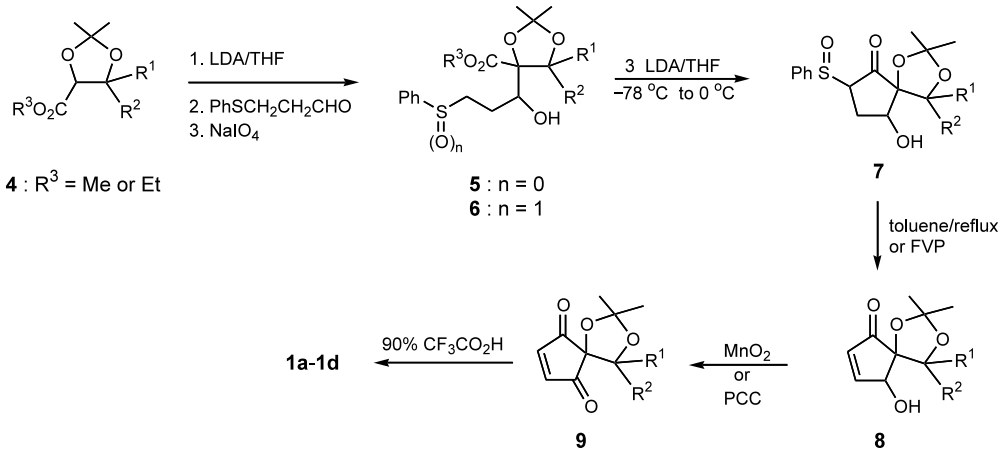

Scheme 1.

Table 1. Preparation of compounds **1**, **5**, **6**, **7**, **8** and **9**

Entry	R^1	R^2	R^3	Yield (%)[a]						
				5	**6**	**7**	**8**	Diastereomeric ratio	**9**	Dehydropentenomycins **1**
1	**a**: H	H	Me	45–63	Quant.[b]	55 (69)[c]	87[d] 73[e]	54:33[f]	76[h]	Quant.[b]
2	**b**: Me	Me	Et	60	70 (55)[c]	66	50[d] 60[e]	29:21[f]	78	92
3	**c**: H	Et	Et	72	76 (56)[c]	77–84	62[d] 65[e] 51[e]	–[g]	84	89
4	**d**: H	Pr*i*	Me Et	89 75	70 74	87 78	71[d] 51[e]	–[g]	77	88

[a] Yield of the isolated product after preparative thin-layer chromatography (SiO_2).
[b] Yield of the crude product.
[c] Yield was calculated based on compound **5**.
[d] Flash vacuum pyrolysis of compound **7** was carried out at 340°C (0.01–0.08 mmHg).
[e] Obtained by refluxing in dry toluene/anhyd. $CaCO_3$/10–12 h.
[f] The diastereomeric ratio of the more polar isomer:less polar isomer was determined after chromatography.
[g] The ratio could not be determined.
[h] MnO_2 in CH_2Cl_2 was employed.

isolated yields. Oxidation of diastereomeric mixtures of **5** to the corresponding spiroenediones **9** was successfully accomplished by employing MnO_2 (2 equiv.)/CH_2Cl_2, rt, overnight for **9a**[7] or pyridinium chlorochromate [PCC (3 equiv.)/CH_2Cl_2, rt, 6 h] for **9b–d**. Good yields (76–84%) of the oxidation products **9a–d** were obtained. Direct oxidation of **7a** leading to the expected product **9a** via 5-phenylsufinylspirocyclopenta-1,3-diones followed by sulfoxide elimination was also investigated by using Collin's reagent, pyridinium chlorochromate (PCC), pyridinium dichromate (PDC) and Swern oxidation. However, all reactions gave unsatisfactory results; only a trace amount of the expected product **9a** could be obtained. Hydrolysis of spiroenedione **9a** with 90% trifluoroacetic acid at 0°C for 3 h afforded (±)-dehydropentenomycin (**1a**)[8] in 88% yield after chromatography on silica gel (EtOAc). Similarly, the analogues **1b–d**[9] of (±)-dehydropentenomycin (**1a**) could be obtained from **9b–d** in good yields under the same conditions. The results are summarized in Table 1.

In conclusion, (±)-dehydropentenomycin (**1a**) and its analogues **1b–d** were synthesized starting from the esters **4** by employing the intramolecular acylation of α-sulfinylcarbanions followed by sulfoxide elimination as the key reactions. The procedure provides a convenient route to this important class of compounds.

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References

1. Noble, M.; Noble, D.; Fletton, R. A. *J. Antibiot*. **1978**, *31*, 15–18.
2. (a) Umino, K.; Furama, T.; Matzuzawa, N.; Awataguchi, Y.; Ito, Y.; Okuda, T. *J. Antibiot*. **1973**, *26*, 506–512; (b) Umino, K.; Takeda, N.; Ito, Y.; Okuda, T. *Chem. Pharm. Bull*. **1974**, *22*, 1233–1238.
3. Bernillon, J.; Favre-Bonvin, J.; Pommier, M. T.; Arpin, N. *J. Antibiot*. **1989**, *42*, 1430–1432.
4. (a) Branca, S.; Smith, A. B., III *J. Am. Chem. Soc*. **1978**, *100*, 7767–7768; (b) Smith, A. B., III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem*. **1982**, *47*, 1855–1869; (c) Verlaak, J. M. J.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett*. **1982**, *23*, 5463–5466; (d) Hetmanski, M.; Purcell, N.; Stoodley, R. J.; Palfreyman, M. N. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2089–2096; (e) Johnson, C. R.; Barbachyn, M. R. *J. Am. Chem. Soc*. **1984**, *106*, 2459–2461; (f) Achab, S.; Coson, J.-P.; Das, B. C. *J. Chem. Soc., Chem. Commun*. **1984**, 1040–1041; (g) Pohmakotr, M.; Popuang, S. *Tetrahedron Lett*. **1991**, *32*, 275–278; (h) Sugahara, T.; Ogasawara, K. *Synlett* **1999**, 419–420; (i) Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett*. **2000**, *41*, 4291–4293; (j) Gallos, J. K.; Damianou, K. C.; Dellios, C. C. *Tetrahedron Lett*. **2001**, *42*, 5769–5771.
5. (a) Pohmakotr, M.; Popuang, S.; Chancharunee, S. *Tetrahedron Lett*. **1989**, *30*, 1715–1718; (b) Pohmakotr, M.; Popaung, S. *Tetrahedron Lett*. **1990**, *31*, 3783–3784.
6. Ladner, W. *Chem. Ber*. **1983**, *116*, 3413–3426 and references cited therein.
7. The oxidation of **8a** using PCC to lead to **9a** gave less satisfactory results.
8. The spectral data of **1a** were consistent with the reported values.[4b]
9. All new compounds gave spectral and analytical data consistent with the proposed structures. Selected NMR and physical data are listed.

   Compound **9a**: a yellow solid; mp 69–70°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.51 [s, 6H, $C(CH_3)_2$], 4.03 (s, 2H, CH_2O), 7.30 (s, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.35, 148.90, 114.54, 78.51, 69.59, 25.83. IR (Nujol): ν_{max} 1722, 1710, 1564, 1461, 1380, 1370, 1330, 1302, 1259, 1231, 1215, 1163, 1112, 1075, 1062, 1028, 861, 834 cm^{-1}. MS m/z (%): 182 (M^+, 23), 167 (51), 164 (22), 139 (29), 124 (66), 96 (57), 82 (72), 68 (55), 59 (91), 54 (74), 43 (100), 39 (29), 31 (4). Anal. calcd for $C_9H_{10}O_4$: C, 59.33; H, 5.53. Found: C, 59.41; H, 5.86%.

   Compound **9b**: a pale yellow solid; mp 96–97°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23, 1.57 [each s, 12H, 2×$C(CH_3)_2$], 7.27 (s, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$): 198.89, 148.84, 112.79, 87.07, 83.44, 28.80, 25.92. IR (neat): ν_{max} 1757, 1714, 1565, 1469, 1371, 1331, 1250, 1218, 1195, 1133, 1055, 1017, 856, 837, 744, 687 cm^{-1}. MS m/z (%): 210 (M^+, 0.75), 166 (61), 151 (21), 149 (14), 138 (17), 123 (14), 111 (10), 94 (10), 82 (100), 69 (13), 55 (12), 43 (30). Anal. calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.08; H, 6.44%.

   Compound **9c**: a yellow solid; mp 66–67°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, J=7.37 Hz, 3H, $CHCH_2CH_3$), 1.23–1.29 and 1.46–1.61 (each m, 2H, $CHCH_2CH_3$), 1.49 and 1.54 [each s, 6H, $C(CH_3)_2$], 4.08 (dd, J=9.23, 4.00 Hz, 1H, $OCHCH_2CH_3$), 7.27 and 7.30 (each d, J=6.49 and 6.57 Hz, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.46, 149.15, 148.83, 112.49, 82.68, 81.44, 26.87, 25.85, 22.67, 10.90. IR (Nujol): ν_{max} 1709, 1328, 1255, 1223, 1177, 1112, 1057, 1004, 921, 886, 841, 816, 788 cm^{-1}. MS m/z (%): 210 (0.19), 195 (12), 153 (25), 152 (95), 137 (9), 125 (11), 124 (35), 112 (8), 97 (12), 96 (46), 95 (20), 94 (45), 82 (63), 70 (25), 69 (50), 59 (24), 55 (16), 54 (53), 53 (16), 43 (100), 39 (38), 38 (72). Anal. calcd for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.13; H, 6.29%.

   Compound **9d**: a pale yellow solid; mp 50–51°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.55 and 0.96 [each d, J=6.69 and 6.52 Hz, 6H, $CH(CH_3)_2$], 1.46 and 1.49 (each s, 6H, $C(CH_3)_2$), 1.79–187 (m, 1H, $CH(CH_3)_2$, 3.90 [d, J=9.84 Hz, 1H, $OCHCH(CH_3)_2$], 7.30 (s, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.71, 200.61, 149.83, 148.84, 111.74, 86.35, 78.58, 28.06, 26.76, 25.65, 20.36, 18.72. IR (Nujol): ν_{max} 1708, 1563, 1334, 1325, 1268, 1251, 1224, 1174, 1121, 1105, 1065, 1033, 977, 890, 850, 807, 770, 722 cm^{-1}. MS m/z (%): 224 (M^+, 0.87), 205 (4), 149 (100), 123 (2), 122 (2), 121 (3), 105 (3), 104 (6), 93 (3), 76 (6), 65 (3), 57 (3), 41 (12).

   Compound **1a**: viscous liquid. ^{1}H NMR (300 MHz, acetone-d_6): δ 3.76 (s, 2H, CH_2O), 4.54–4.66 (br s, 2H, OH, CH_2OH), 7.41 (s, 2H, CH=CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 204.72, 150.48, 74.90, 64.36. IR (Neat): ν_{max} 3444 (br), 1755, 1713 1643, 1563, 1342, 1332, 1127, 1059, 979, 913, 864 cm^{-1}. MS m/z (%): 142 (M^+, 3), 124 (85), 112 (24), 83 (29), 82 (69), 68 (24), 55 (100), 53 (23), 42 (42). The data are in good agreement with the literature.[4b]

   Compound **1b**: mp 111–112°C. ^{1}H NMR (300 MHz, acetone-d_6): δ 1.30 [s, 6H, $C(CH_3)_2$], 7.39 (s, 2H, CH=CH). ^{13}C NMR (75 MHz, acetone-d_6): δ 204.54, 149.95, 79.04, 74.30, 25.16. IR (KBr): ν_{max} 3450 (br), 1746, 1702, 1562, 1460, 1396, 1383, 1358, 1325, 1261, 1162, 1183, 1138, 1118, 1053, 988, 947, 855, 836 cm^{-1}. MS m/z (%): 152 (M^+-H_2O, 24), 112 (62), 84 (15), 69 (11), 59 (100), 55 (27), 43 (49).

   Compound **1c**: mp 177°C (dec.). ^{1}H NMR (300 MHz, acetone-d_6): δ 0.93 (t, J=7.37 Hz, 3H, CH_2CH_3), 1.41–1.56 and 1.83–2.01 (each m, 2H, CH_2CH_3), 2.00–3.60 (br, 2H, OH), 3.70 (dd, J=10.43, 2.11 Hz, 1H, $CHCH_2CH_3$), 7.41 and 7.44 (each d, J=6.41 and 6.41 Hz, 2H, CH=CH). ^{13}C NMR (75 MHz, acetone-d_6): δ 205.54, 204.04, 150.52, 149.98, 77.02, 76.12, 24.33, 10.95. IR (Nujol): ν_{max} 3420 (br), 1745, 1709, 1563, 1358, 1325, 1261, 1202, 1183, 1137, 1118, 1053, 989, 947, 855, 836, 699 cm^{-1}. MS m/z (%): 172 (M^++2, 0.70), 82 (15), 59 (36), 54 (80), 43 (100).

   Compound **1d**: mp 182°C (dec.). ^{1}H NMR (300 MHz, acetone-d_6): δ 0.76 and 0.90 [each d, J=6.64 and 6.72 Hz, 6H, $CH(CH_3)_2$], 1.93–2.02 [m, 1H, $CH(CH_3)_2$], 3.51 [d, J=5.23 Hz, 1H, $CHCH(CH_3)_2$], 4.73 (br t, 2H, CHO-HCOH), 7.31 (br s, 2H, CH=CH). ^{13}C NMR (75 MHz, acetone-d_6) 205.01, 203.81, 150.40, 149.76, 78.70, 78.11, 30.28, 21.60, 18.15. IR (KBr): ν_{max} 3424 (br), 1753, 1630, 1384, 1072 cm^{-1}. MS m/z (%) 185 (M^++1, 0.10), 166 (25), 142 (8), 141 (10), 113 (24), 112 (100), 82 (24).