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Total Synthesis of Angucyclines. Part 13:[1] Biomimetic-type Approach to a Potential Precursor of the Landomycinone Angucyclinone

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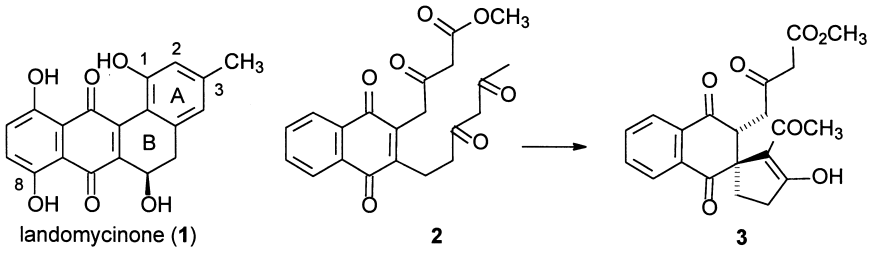
Abstract—The dimethoxy naphthalene derivative **10** with two vicinal side chains was prepared by reaction of the dibromide **7** with silyl ether **8** ($[Bu_4N][Ph_3SnF_2]$-catalysis) followed by Stille reaction of **9** with stannane **5**. Acidic hydrolysis gave the triketo ester **11** that cyclized in a biomimetic-type reaction to the highly substituted dihydro benz[*a*]anthracene **12**, a potential precursor of the angucyclinone landomycinone.

The landomycins, discovered by Rohr et al.[2] are members of the glycosidic angucycline antibiotics that show an unusual spectrum of antitumor activities.[3] They differ in the composition of the oligodeoxy sugars, glycosidically linked to 8-OH with landomycinone (**1**) (Scheme 1) as the common aglycon. The hexasaccharide fragment of landomycin A was recently synthesized by Sulikowski et al.[4] However, no synthesis of the aglycone **1** has yet been published. One of the special features of **1** is the aromatic ring A and an hydroaromatic ring B. In most of the structurally more simple aromatic angucyclinones (for reviews see Refs. 5,6), landomycinone (**1**) employing a biomimetic-type methodology. The common feature of this synthesis is the cyclization of oligo ketides such as **2** in which two vicinal side chains are attached on a quinoide core. Members of the aromatic angucylines such as rabelomycin[7] as well as the pentacyclic benz[*a*]naphthacene G-2N[8] have been synthesized using this method. In this latter reaction, with a β-keto ester present as the top side chain, spontaneous aromatization of ring A occurred in contrast to aldol cyclizations with a 2-oxopropyl top side chain without an ester group.[7] Thus, the objective of the present work was to see if a similar



Scheme 1. Structure of landomycinone (**1**)[2] and spirocyclization of triketo ester **2** to **3**.

ring B is unsaturated which also corresponds to the thermodynamically most stable form of unsaturated benz[*a*]anthraquinones.

We now disclose a novel approach towards the synthesis of behavior could be realized in the tetracyclic series to approach angucyclines of the landomycin type.

However, surprisingly, the naphthoquinone triketo ester **2** cyclized to the spiro compound **3** upon treatment with base as shown in Scheme 1.[9] To avoid intramolecular addition to the quinoide Michael acceptor, we decided to study the reaction of the corresponding hydroquinone dimethyl ether. A straightforward method for attachment of the top side chain was the Stille reaction[10] of bromides with functionalized allylstannans such as **5**. Steric hindrance in the

Keywords: Stille reaction; naphthalene derivatives; landomycins angucyclinone.

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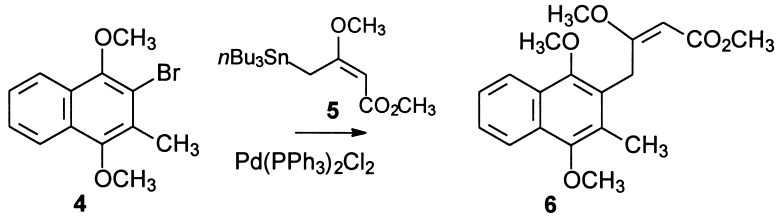
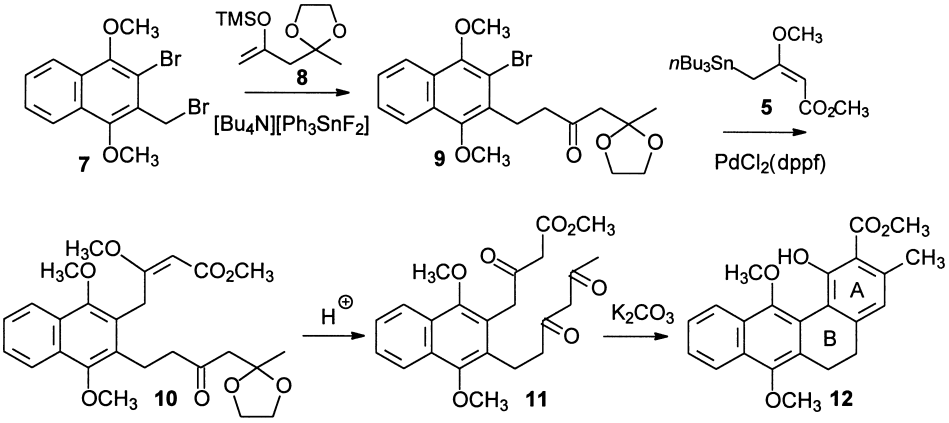


Scheme 2. Stille coupling of the model compound **4** with the stannane **5**.



Scheme 3. Attachment of the side chains and ring closure of the triketo ester **11** to benz[*a*]anthracene **12**.

dimethyl ethers is greater than in the corresponding naphthoquinones and we therefore first studied the Stille reaction with the model compound **4** (Scheme 2).

Much to our delight, the reaction of **4** and **5** proceeded without difficulty and gave the substituted naphthalene **6** in 88% yield. In previous studies, it was advantageous to attach the bottom side chain first.[7] Therefore, the known dibromide[7,11] was coupled in a procedure according to Gingras[12] with the enolsilyl ether **8**, prepared in a kinetically controlled silylation reaction with the pentane-2,4-dione monoketal. Tetrabutylammonium difluorotriphenylstannate ($[Bu_4N][Ph_3SnF_2]$) was used as a new anhydrous synthetic equivalent to tetrabutyl ammonium fluoride in this coupling reaction with the bromide **7** to generate the enolate from the silyl ether **8**. The procedure is shorter than the previously used alkylation with β-keto esters[7] and the steps of saponification and decarboxylation are avoided. The adduct **9** was isolated in 90% yield and was directly used for the attachment of the top side chain in the Stille reaction with the stannane **5** (Scheme 3). In view of the greater steric hindrance of the long bottom side chain, the yield of **10** in the not optimized reaction was only 38%. Treatment of **10** with hydrochloric acid cleaved simultaneously the enol ether and the ketal to give the triketo ester **11** in 58% combined yield. ^{1}H NMR measurements revealed that 81% of the compound **11** was enolized in $CDCl_3$ solution. Finally, the aldol reaction of **11** was studied using the mild base potassium carbonate in 2-propanol. In a smooth reaction, only one of the two possible cyclization modes[13] was realized to afford an unpolar compound of the angularly condensed tetracyclic structure **12** in 66 % yield.

The synthetic sequence comprises two successive aldol reactions and elimination of two molecules of water. As expected, the autoxidation of the dihydro compound that easily occurred with dihydroanthraquinones did not take place with the hydroquinone dimethyl ether. Thus, the biomimetic-type reactions described here have great potential for the construction of the landomycin or elmycin aglycones with nonaromatic ring B.

Experimental

Methyl (*E*)-4-(1,4-dimethoxy-3-methylnaphthalen-2-yl)-3-methoxy-2-butenoate (6). A solution of naphthalene **4**[14] (300 mg, 1.07 mmol), $Pd(PPh_3)_2Cl_2$ (38 mg, 54 μmol), CuBr (156 mg, 1.09 mmol), and the (*E*)-stannane **5**[9] (900 mg, 2.15 mmol) in dry 1,4-dioxane (5 ml) was refluxed under argon for 6 h (TLC monitoring). The cooled mixture was then filtered through a short column of silica gel (Et_2O) and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (1, PE; 2, CH_2Cl_2) to afford **6** (298 mg, 84%) as a yellow oil. IR (KBr): $\tilde{\nu}$=2940 cm^{-1} (C–H), 2829 (C–H), 1706 (C=O), 1608. UV (methanol): λ_{max} (log ϵ)=292 nm (3.71), 326 (3.08). ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.33 (s, 3 H, CH_3), 3.51 (s, 3 H, aliph. OCH_3), 3.76 (s, 3 H, aliph. OCH_3), 3.85 (s, 3 H, arom. OCH_3), 3.88 (s, 3 H, arom. OCH_3), 4.57 (s, 2 H, 4-H), 5.17 (s, 1 H, 2-H), 7.41–7.50 (m, 2 H, 6′-H and 7′-H), 8.00–8.10 (m, 2 H, 5′-H and 8′-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=12.93 (q, CH_3), 30.04 (t, C-4), 51.35, 56.26 (2×q, 2×aliph. OCH_3), 61.75, 62.60 (2×q, 2×arom. OCH_3), 91.04 (d, C-2), 122.59, 122.87 (2×d, C-5′ and C-8′), 125.71, 126.12 (2×d, C-6′ and C-7′), 126.76, 127.40, 127.87, 128.35 (4×s, C-2′, C-3′, C-4a′ and C-8a′), 150.18, 151.39 (2×s, C-1′ and C-4′), 168.68, 174.26 (2×s, C-1 and C-3). MS (EI/125°C): *m/z* (%): 330 (100) [M^+], 298 (36) [M^+-CH_3OH], 283 (50) [$M^+-CH_3OH-CH_3$], 255 (29)

[M^+–CO_2CH_3–CH_3–1], 239 (33) [M^+–CO_2CH_3–OCH_3–1], 225 (33), 224 (23), 209 (14), 181 (22), 152 (9), 105 (13), 59 (18) [$CO_2CH_3^+$], 15 (47) [CH_3^+]. HRMS: $C_{19}H_{22}O_5$; Calcd 330.1467; found 330.1474±3 ppm.

3-(2-Methyl-[1,3]dioxolan-2-yl)-2-trimethylsilyloxy-1-propene (8). A solution of *n*-BuLi (10.73 ml, 1.3 M in hexane, 76.34 mmol) was added under argon to a solution of diisopropylamin (7.73 g, 76.34 mmol) in dry THF. This LDA solution was added slowly at −78°C to a solution of the pentane-2,4-dione monacetal (10.00 g, 69.40 mmol) and stirred for 1 h. TMSCl (7.54 g, 69.40 mmol) was then slowly added and stirring was continued for 2 h at −78°C. The reaction was quenched by addition of a saturated aqueous NH_4Cl solution (80 ml) and the aqueous phase was extracted twice with Et_2O (2×40 ml). The combined organic phases were washed with water (40 ml), dried (Na_2SO_4), the solvent was removed under reduced pressure, and the residue distilled at 90–95 °C to afford the silyl ether **8** (12.9 g, 86%), bp 90–95°C/13–15 Torr. The compound with internal double bond was present to ca. 30% according to ^{1}H NMR. ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.22 (s, 9 H, $OSi(CH_3)_3$), 1.42 (s, 3 H, dioxolane–CH_3), 2.34 (s, 2 H, 3-H), 3.95 (s, 4 H, OCH_2CH_2O), 4.15 (s, 2 H, 1-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=0.42 (q, $OSi(CH_3)_3$), 24.36 (q, dioxolane–CH_3), 46.04 (t, C-3), 64.60 (t, OCH_2CH_2O), 93.62 (t, C-1), 110.35 (s, dioxolane–OCO), 155.62 (s, C-2).

4-(3-Bromo-1,4-dimethoxynaphthalen-2-yl)-1-(2-methyl-[1,3]dioxolan-2-yl)-butan-2-one (9). The silylenol ether **8** (1.26 g, 5.83 mmol) was added at −78°C under argon to a solution of the dibromide **7** (700 mg, 1.94 mmol) in dry THF (10 ml). Tetrabutylammonium difluorotriphenylstannate ([Bu_4N][Ph_3SnF_2])[12] (1.47 g, 2.33 mmol) was then added in one portion. After 10 min of stirring at −78°C, the mixture was allowed to warm to 20°C and stirring was continued for 2.5 h (TLC control). The mixture was then filtered through a short column of silica gel (CH_2Cl_2) and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (PE/AcOEt 2:1) to yield 799 mg (90%) adduct **9** as an oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.45 (s, 3 H, dioxolane–CH_3), 2.81 (s, 2 H, 1-H), 2.85–2.90 (m, 2 H, 4-H), 3.20–3.27 (m, 2 H, 3-H), 3.91 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.97 (s, 4 H, OCH_2CH_2O), 7.47–7.58 (m, 2 H, 6′-H and 7′-H), 8.00–8.12 (m, 2 H, 5′-H and 8′-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=24.95 (t, C-4), 25.05 (q, dioxolane–CH_3), 44.34 (t, C-3), 52.02 (t, C-1), 61.76, 62.93 (2×q, 2×OCH_3), 65.08 (t, OCH_2CH_2O), 108.34 (s, dioxolane–OCO), 116.66 (s, C-3′), 122.96 (2×d, C-5′ and C-8′), 126.93, 127.10 (2×d, C-6′ and C-7′), 128.27, 128.35 (2×s, C-4a′ and C-8a′), 130.46 (s, C-2′), 150.55, 151.14 (2×s, C-1′ and C-4′), 207.07 (s, C-2).

Methyl (*E*)-4-{1,4-dimethoxy-3-[4-(2-methyl-[1,3]dioxolan-2-yl)-3-oxo-butyl]-naphthalen-2-yl}-3-methoxybut-2-enoate (10). A solution of the bromide **9** (120 mg, 0.28 mmol), dichloro[1,1′bis(diphenylphosphino)ferroceno]-palladium(II) [$PdCl_2$(dppf)][15] (21 mg, 28 μmol), CuBr (61 mg, 0.43 mmol), (*E*)-stannyl ester **5** (352 mg, 0.85 mmol) in dry 1,4-dioxane (4 ml) was refluxed under argon for 17 h. Additional $PdCl_2$(dppf) (2×5 mg) was added after 4 and 9 h. The solution was filtered through a short column of silica gel (Et_2O), the solvent was removed under reduced pressure, and the residue purified by column chromatography on silica gel (1, PE; 2, Et_2O/PE 2:1) to afford 32 mg (27%) of the starting material **8** and 39 mg (38% by conversion) of the bisalkylated product **10** as an oil. IR (KBr): $\tilde{\nu}$=2945 cm^{-1} (C–H), 1707 (C=O), 1612 (C=O), 1444, 1360, 1287, 1187, 1140 (C–O), 1051, 962, 778. UV (methanol): λ_{max} (log ϵ)=287 nm (3.99), 327 (3.41). ^{1}H NMR (200 MHz, $CDCl_3$): δ=1.44 (s, 3 H, dioxolane–CH_3), 2.72–2.77, 2.91–3.03 (2×m, 6 H, 1″-H, 2″-H and 4″-H), 3.53 (s, 3 H, aliph. OCH_3), 3.74 (s, 3 H, aliph. OCH_3), 3.89 (s, 6 H, 2×arom. OCH_3), 3.94 (s, OCH_2CH_2O), 4.57 (s, 2 H, 4-H), 5.15 (s, 1 H, 2-H), 7.45–7.50 (m, 2 H, 6′-H and 7′-H), 7.96–8.04 (m, 2 H, 5′-H and 8′-H). ^{13}C NMR (50 MHz, $CDCl_3$): δ=21.66 (t, C-1″), 24.85 (q, dioxolane–CH_3), 29.18 (t, C-4), 45.04 (t, C-2″), 51.39 (q, aliph. OCH_3), 52.03 (t, C-4″), 56.15 (q, aliph. OCH_3), 62.43, 62.62 (2×q, 2×arom. OCH_3), 65.00 (t, OCH_2CH_2O), 91.19 (d, C-2), 108.31 (s, dioxolane–OCO), 122.66, 123.04 (2×d, C-5′ and C-8′), 125.96 (d, C-6′ or C-7′), 126.15 (s, C-2′, C-3′, C-4a′ or C-8a′), 126.21 (d, C-6′ or C-7′), 127.80, 128.33, 131.04 (3×s, C-2′, C-3′, C-4a′ or C-8a′), 150.66, 151.76 (2×s, C-1′ and C-4′), 168.69, 174.05 (2×s, C-1 and C-3), 207.38 (s, C-3″). (MS (EI/175°C): *m/z* (%): 472 (68) [M^+], 323 (14), 295 (10), 239 (9), 129 (10), 87 (100) [$H_3CC(OCH_2CH_2O)^+$], 43 (48) [$COCH_3^+$]. HRMS: $C_{26}H_{32}O_8$; Calcd: 472.2097; Found 472.2091±3 ppm.

Methyl 4-[3-(3,5-dioxo-hexyl)-1,4-dimethoxy-naphthalen-2-yl]-3-oxo-butanoate (11). A solution of the dimethoxynaphthalene **10** (54 mg, 0.11 mmol) in CH_2Cl_2 (6 ml) was treated with 3 drops of conc. HCl and stirred for 3.5 h (TLC monitoring). The reaction mixture was then poured into water, the aqueous phase was extracted with CH_2Cl_2 (10 ml), the combined organic phases were dried (Na_2SO_4), and the solvent removed under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 100:1) to yield 27.4 mg (58%) of the triketo ester **11** as a yellow solid, mp: 78.5°C. According to ^{1}H NMR 81% of the compound **11** was enolized in $CDCl_3$ solution. IR (KBr): $\tilde{\nu}$=2951 cm^{-1} (C–H), 2932 (C–H), 2840 (C–H), 1743 (C=O), 1704 (C=O), 1632 (C=C), 1589 (C=C), 1454, 1406, 1358 (C–O), 1329 (C–O). UV (methanol): λ_{max} (log ϵ)=283 nm (4.00), 328 (2.94). ^{1}H NMR (200 MHz, $CDCl_3$) (enol form): δ=2.05 (s, 3 H, 6″-H), 2.49–2.57 (m, 2 H, 1″-H), 2.91–3.09 (m, 2 H, 2″-H), 3.63 (s, 2 H, 2-H), 3.74 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 4.14 (s, 2 H, 4-H), 5.51 (s, 1 H, 5″-H), 7.48–7.53 (m, 2 H, 6′-H and 7′-H), 8.01–8.07 (m, 2 H, 5′-H and 8′-H), 15.43 (br s, 1 H, chel. OH). ^{13}C NMR (50 MHz, $CDCl_3$) (enol): δ=23.89 (t, C-1″), 25.13 (q, C-6″), 39.19 (t, C-2″), 42.17 (t, C-4), 48.83 (t, C-2), 52.86 (q, Ester–OCH_3), 62.43 (br q, 2×arom. OCH_3), 100.37 (d, C-5″), 122.86, 122.96 (2×d, C-5′ and C-8′), 123.38 (s, C-2′, C-3′, C-4a′ or C-8a′), 126.36, 126.72 (2×d, C-6′ and C-7′), 127.86, 128.77, 129.84 (s, C-2′, C-3′, C-4a′ or C-8a′), 151.17, 151.46 (2×s, C-1′ and C-4′), 168.12 (s, C-1), 191.09, 193.99 (2×s, C-3″ and C-5″), 201.19 (s, C-3). MS (EI/159°C): *m/z* (%): 414 (100) [M^+], 382 (13) [M^+–CH_3OH], 340 (17) [M^+–$CH_2CO_2CH_3$–1], 297 (30), 255 (28), 227 (35), 213 (18), 181 (12), 141 (15), 115 (11) [$CH_2COCH_2CO_2CH_3^+$], 85 (28) [$COCH_2COCH_3^+$], 43 (38) [$COCH_3^+$]. HRMS: $C_{23}H_{26}O_7$; Calcd 414.1679; Found: 414.1686±3 ppm.

Methyl 1-hydroxy-7,12-dimethoxy-3-methyl-5,6-dihydrobenz[*a*]anthracene-2-carboxylate (12). A solution of the triketone **11** (19.8 mg, 0.048 mmol) in dry 2-propanol (3 ml) and dry CH_2Cl_2 (0.5 ml) was treated with dry K_2CO_3 (80 mg, 0.579 mmol) and the suspension was stirred at 20°C for 20 h (TLC monitoring). The solution was acidified by addition of 1 M HCl (1.5 ml) and saturated NH_4Cl solution (15 ml). The aqueous phase was extracted with CH_2Cl_2 (10 ml), dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 100:1) to afford 12 mg (66%) of the tetracycle **11** as a resin. IR (KBr): $\tilde{\nu}$=3147 cm^{-1} (OH), 2924 (C–H), 2841 (C–H), 1727 (C=O, ester), 1616, 1582. UV (methanol): λ_{max} (log ϵ)=270 nm (3.78), 301 (3.35). ^{1}H NMR (200 MHz, $CDCl_3$): δ=2.38 (s, 3 H, CH_3), 2.70–2.77 (m, 2 H, 5′-H or 6′-H), 2.95 (br s, 2 H, 5′-H or 6′-H), 3.75 (s, 3 H, arom. OCH_3), 3.89 (s, 3 H, arom. OCH_3), 3.97 (s, 3 H, aliph. OCH_3), 6.78 (s, 1 H, 4′-H), 7.52–7.60 (m, 2 H, 9′-H and 10′-H), 8.09–8.17 (m, 2 H, 8′-H and 11′-H), 9.48 (s, 1 H, OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ=20.16 (q, CH_3), 23.93, 31.20 (2×t, C-5′ and C-6′), 52.60 (q, aliph. OCH_3), 62.22, 62.81 (2×q, 2×arom. OCH_3), 118.81 (s, C-12b′), 121.94, 122.40 (2×d, C-4′, C-8′ or C-11′), 122.64 (s, C-4a′, C-6a′, C-7a′, C-11a′ or C-12a′), 122.75 (d, C-4′, C-8′ or C-11′), 122.89 (s, C-4a′, C-6a′, C-7a′, C-11a′ or C-12a′), 126.64, 127.02 (2×d, C-9′ and C-10′), 128.09, 128.61, 129.60 (3×s, C-4a′, C-6a′, C-7a′, C-11a′ or C-12a′), 137.25 (s, C-2′), 143.54 (s, C-3′), 147.47, 149.36 (2×s, C-7′ and C-12′), 152.90 (s, C-1′), 170.26 (s, C-1). MS (EI/155°C): *m*/*z* (%): 378 (100) [M^+], 331 (80), 303 (17), 260 (11), 202 (16), 173 (9), 157 (12), 43 (2), 18 (46) [H_2O]. HRMS: Calcd for $C_{23}H_{22}O_5$: 378.1467; Found 378.1473±3 ppm.

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