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Preliminary Communication

Synthesis of Macrotetrolide α, a Designed Polynactin Analog Composed of (+)- and (−)-Bishomononactic Acids

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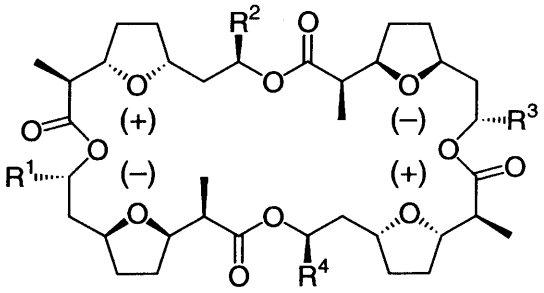
Macrotetrolide α, a designed analog of polynactin composed of (+)- and (−)-bishomononactic acids, was synthesized. These monomers were prepared *via* optical resolution of the corresponding (*S*)-*O*-acetylmandelates. Assembly of the monomers to macrotetrolide α took seven steps without any loss of the intermediates.

Key words: total synthesis; polynactin; macrotetrolide; bishomononactate; optical resolution

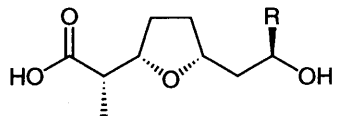
The polynactin family (**1**) of macrotetrolide ionophore antibiotics, which have been isolated from various *Streptomyces* species,[1,2] is composed of both enantiomers of monomeric acids **2a**, **2b** and **2c** arranged in an alternating order (Fig. 1). Their interesting structures have led many chemists to synthesize these monomers and tetramers.[3,4] A mixture of the parts (**1a–1e**) is used as an acaricide for fermentative production. Nonactin (**1a**) has recently attracted considerable attention because it showed strong inhibitory activity toward the multi-drug-resistant cell with P170 sugar protein,[5] while an immunosuppressive effect has been observed for tetranactin (**1e**).[6] Although there is no information about the biological activities of macrotetrolides B-G (**1f–1i**),[2] Lee and Priestly have reported that an imaginary analog composed of four bishomononactate units (**1j**) had been calculated to show stronger K^+ binding ability than nonactin (**1a**).[7] Since the K^+ affinity was found to be highly correlated with the biological activity,[7,8] we planned to synthesize this analog (**1j**), named macrotetrolide α, for biological studies. In the previous paper, we have reported the synthesis of the (±)-**2c** methyl ester,[4] and we describe here the optical resolution of (±)-**2c** and the total synthesis of **1j**.

To prepare (+)- and (−)-**2c**, we first attempted asymmetric reduction of their synthetic intermediates;[4] however, these attempts gave poor results. Instead, we applied the chromatographic separation of diastereomers reported by Wang and Metz (Scheme 1).[9] They resolved (±)-**2a** as (*S*)-*O*-acetylmandelic ester, and for the later condensation steps, we prepared (±)-**2c** as its benzyl esters **3**. In our case, the corresponding diastereomeric esters could be easily separated (R_f = 0.50 and 0.55, hexane/EtOAc = 3:1), and the chiral auxiliary was selectively removed to give both enantiomers of **2c**.[10] We identified the absolute chemistry of (+)- and (−)-**2c** by the signs of the specific optical rotation values and the



polynactin (**1**)

		R^1	R^2	R^3	R^4
nonactin	(**1a**)	Me	Me	Me	Me
monactin	(**1b**)	Me	Me	Me	Et
dinactin	(**1c**)	Me	Et	Me	Et
trinactin	(**1d**)	Me	Et	Et	Et
tetranactin	(**1e**)	Et	Et	Et	Et
macrotetrolide B	(**1f**)	Et	*i*-Pr	Et	*i*-Pr
C	(**1g**)	Et	Me	*i*-Pr	*i*-Pr
D	(**1h**)	Et	Me	Et	*i*-Pr
G	(**1i**)	Et	Me	*i*-Pr	Me
macrotetrolide α	(**1j**)	*i*-Pr	*i*-Pr	*i*-Pr	*i*-Pr



(+)-nonactic acid [(+)-**2a**] R = Me
(+)-homononactic acid [(+)-**2b**] R = Et
(+)-bishomononactic acid [(+)-**2c**] R = *i*-Pr

Fig. 1. Polynactin Family.

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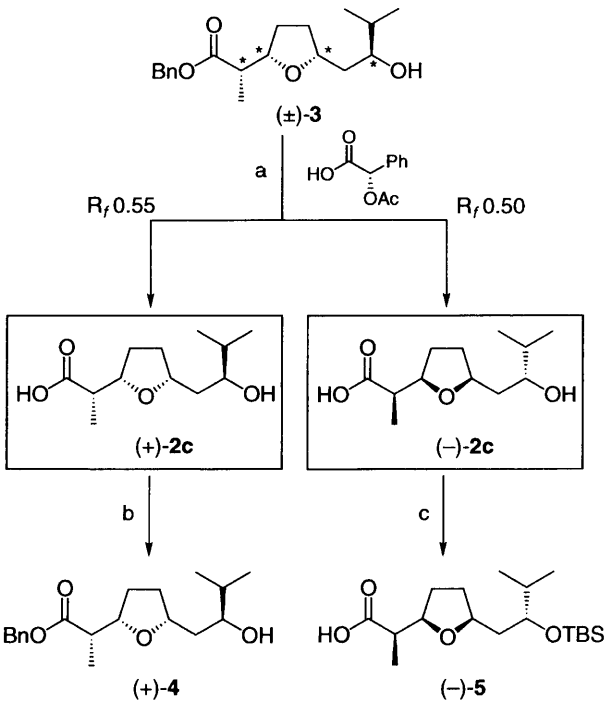
Abbreviations: EDC, *N*-ethyl-*N*′-3-dimethylaminopropylcarbodiimide; HOAt, 1-hydroxy-7-azabenzotriazole

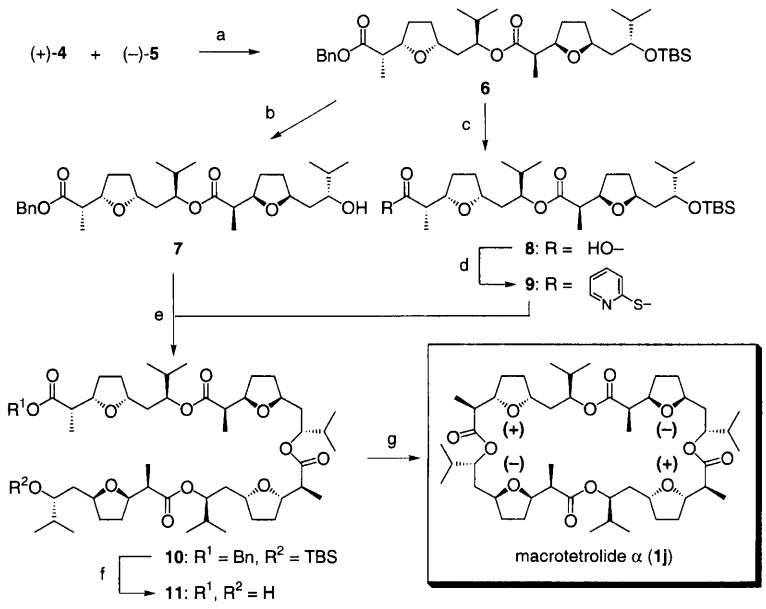
above-mentioned R_f values in comparison with those of **2a**. To prepare the substrates for macrolactonization, (+)-**2c** and (−)-**2c** were respectively converted to (+)-**4** and (−)-**5**.



Scheme 1. Resolution of (±)-Benzyl Bishomononactate.
a) i. (*S*)-*O*-acetylmandelic acid, EDC, DMAP, CH_2Cl_2; ii. SiO_2 separation; iii. 1 N KOH, MeOH-THF [50% for (+)-**2c** and 42% for (−)-**2c**]. b) BnBr, *t*-BuOK, DMF, 65°C (86%). c) i. BnBr, *t*-BuOK, DMF 65°C; ii. TBSCl, Im, THF; iii. H_2, 10% Pd-C, MeOH (81%).

We then condensed (+)-**4** and (−)-**5** to form dimeric compound **6**. The usual conditions applied for nonactic or homononactic acids[3] gave poor results due to the bulky isopropyl substituent. Condensation with such carbodiimides as DCC and EDC only proceeded under vigorous conditions or by adding HOBt or HOAt, the yields being <20%. Mixed anhydride methods were next investigated. In the case of the Mukaiyama-Corey method,[11] condensation did not proceed, although the intermediate pyridyl thioester could be isolated. However, according to Gerlach *et al.*,[12] the addition of $AgClO_4$ promoted and completed the reaction within a few minutes to give desired dimer **6** in an 86% yield. Unreacted (+)-**4** and (−)-**5** were recovered. Dimer **6** was converted to alcohol **7** and then to acid **8** in quantitative yields. Pyridyl thioester **9** derived from **8** was condensed with **7** to give tetramer **10** in a 90% yield. Unreacted starting materials **7** and **8** were completely recovered. Again the TBS and benzyl group of **10** were successively removed in quantitative yields to give hydroxy acid **11**. Finally, macrolactonization by the same method gave macrotetrolide α (**1j**)[13] in an 81% yield. In this step, none of the octamer was detected, and **11** was recovered in a 19% yield. All the reactions were very clear and all the intermediate compounds could be completely recovered in each step, so the total yield of the condensation steps was nearly quantitative.

The novel designed polynactin analog, named macrotetrolide α, was synthesized in an almost quantitative yield by the assembly of (+)-and (−)-bishomononactic acids. Biological studies of macrotetrolide α, and (+)- and (−)-bishomononactic acids



Scheme 2. Synthesis of Macrotetrolide α.
a) i. (−)-**5**, $(PyS)_2$, Ph_3P, toluene, reflux; ii. (+)-**4**, $AgClO_4$ (86%). b) HF, CH_3CN (quant). c) H_2, Pd-C, MeOH (quant). d) $(PyS)_2$, Ph_3P. e) $AgClO_4$ (90%). f) i. HF, CH_3CN; ii. H_2, Pd-C, MeOH (quant). g) i. $(PyS)_2$, Ph_3P; ii. $AgClO_4$ (81%).

are underway.

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10) (+)-**2c**: a colorless oil, $[\alpha]_D^{21}$ +27 (*c* 0.090, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.88-0.92 (3H, d, J= 6.9 Hz, 10-H), 0.92-0.95 (3H, d, J=6.6 Hz, 9-Me), 1.16-1.21 (3H, d, J = 7.1 Hz, 2-Me), 1.24-1.32 (1H, m), 1.60-1.78 (4H, m), 1.98-2.10 (2H, m), 2.46-2.56 (1H, quint, J=7.1 Hz, 2-H), 3.56-3.62 (1H, m, 8-H), 3.94-4.02 (1H, m, 3-H), 4.20-4.28 (1H, m, 6-H). (−)-**2c**: a colorless oil, $[\alpha]_D^{21}$ −27 (*c* 0.080, $CHCl_3$).

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13) Macrotetrolide α (**1j**): a colorless oil, $[\alpha]_D^{24}$ ±0°; (*c*= 0.02, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.86-0.91 (24H, m), 1.07-1.13 (12H, m), 1.40-2.08 (28H, m), 2.48 (1H, m), 2.55-2.67 (3H, m), 3.77-3.88 (3H, m), 3.95 (1H, m), 4.00-4.08 (3H, m), 4.12 (1H, m), 4.80-4.96 (4H, m). FABMS (*m*-nitrobenzyl alcohol + NaCl) *m/z*: 195 (monomeric fragment $+H-H_2O)^+$, 213 (monomeric fragment + H)$^+$, 425 (dimeric fragment + H)$^+$, 850 $(M+H)^+$, 872 $(M+Na)^+$. HR-FABMS *m/z* $(M+H)^+$: calcd. for $C_{48}H_{81}O_{12}$, 849.573; found, 849.573.