Pergamon

Tetrahedron Letters, Vol. 38, No. 34, pp. 6023-6026, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01339-7

A New Tactic for Diastereo- and Enantiocontrolled Synthesis of (–)-Malyngolide *via* Catalytic *Meso*-Asymmetrization

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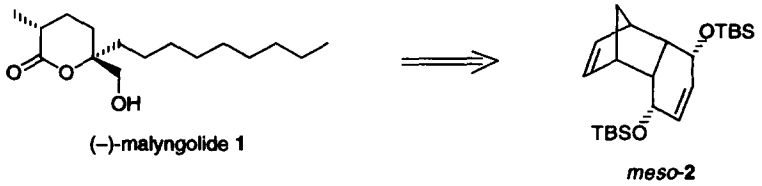
Abstract: A *meso*-1,4-enediol *bis*-silyl ether **2** having bicyclo[2.2.1]heptene background has been transformed diastereo- and enantioselectively into (–)-malyngolide **1**, an antibiotic isolated from the blue-green marine algae, *Lyngbya majuscula*, *via* Rh(I)-(*R*)BINAP-catalyzed asymmetrization and diastereoselective modification of the optically active product thus obtained.

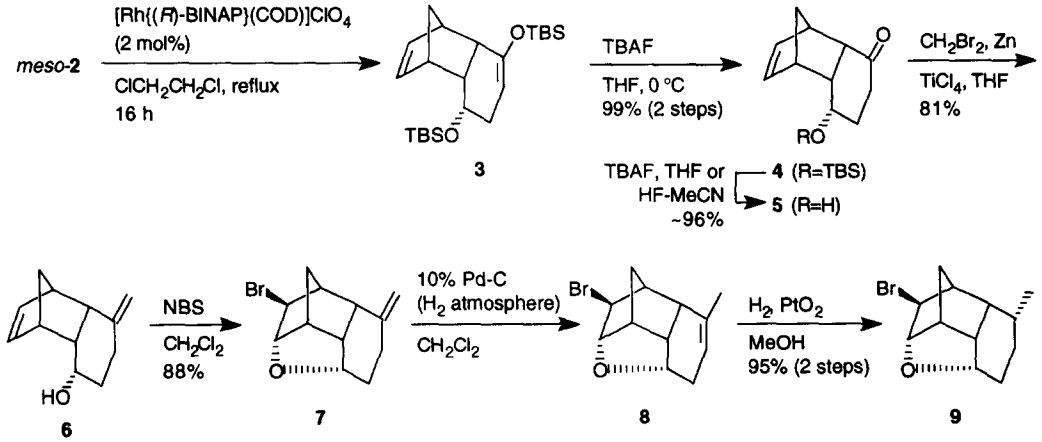
Despite its simple structure having one quaternary and one tertiary stereogenic center on the δ-lactone ring, diastereocontrolled construction of the two centers of (–)-malyngolide[1] **1**, an antibiotic isolated from the blue-green marine algae, *Lyngbya majuscula*, is not an easy task. Although nearly two dozen methods for its chiral synthesis have so far been reported,[2] only a single procedure originally developed by Matsuo and Tanaka[3] in their racemic synthesis has succeeded in installing the two stereogenic centers with satisfactory diastereoselectivity.[4] Thus, two stereogenetic centers were first installed enantio- and diastereoselectively on the cyclopentanone framework and the chiral 2,2,3-trisubstituted cyclopentanone generated was next transformed into (–)-malyngolide **1** by regioselective Baeyer-Villiger oxidation.[2j,2o,2p,2t] We report herein a new tactic leading to high enantio- and diastereocontrolled construction (>96% ee:>99% de) of (–)-malyngolide **1** starting from the *meso*-1,4-enediol *bis*-silyl ether[5] **2** having bicyclo[2.2.1]heptene background by use of a [Rh{(*R*)-BINAP}(COD)]ClO_4 [Rh(I)-(*R*)BINAP][6]-catalyzed *meso*-asymmetrization reaction[5] followed by diastereoselective modification of the optically active product based on its biased stereochemical background (**Scheme 1**).



(–)-malyngolide **1** *meso*-**2**

Scheme 1

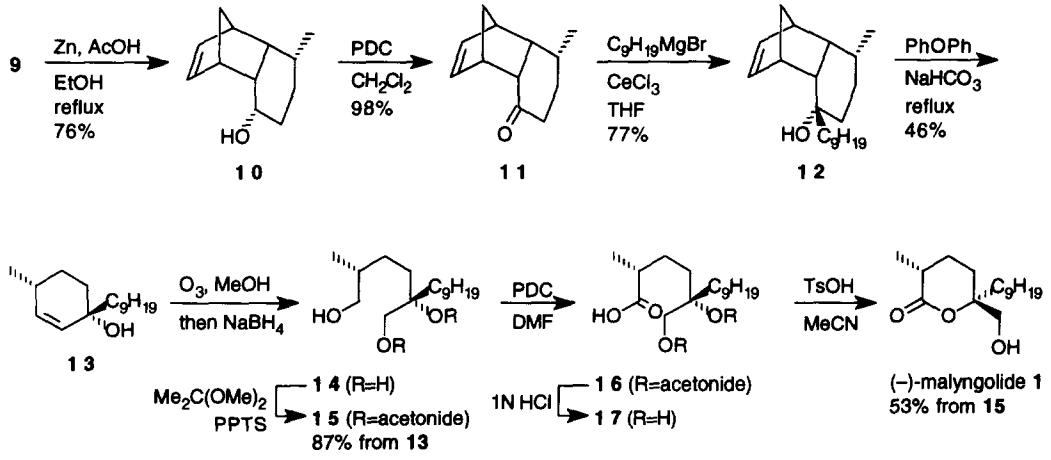
According to the established procedure,[5] the tricyclic *meso-bis*-silyl ether **2** was refluxed in 1,2-dichloroethane in the presence of a catalytic amount of Rh(I)-(*R*)BINAP (2 mol%) for 16 h to give the enol ether **3** which, immediately, was treated with tetrabutylammonium fluoride (TBAF) in THF (0 °C, 10 min) to afford the optically active keto ether **4**, $[\alpha]_D^{30}$ +26.6 (*c* 1.5, $CHCl_3$), in nearly quantitative yield. Desilylation of **4** with TBAF (THF, rt, 20 h) or with a hydrogen fluoride-acetonitrile complex[7] (–30 °C, 24 h) gave the hydroxy ketone **5**, $[\alpha]_D^{29}$ +136.2 (*c* 1.9, $CHCl_3$), excellently, whose benzoate was proved to be 98% ee by hplc analysis using chiral column (CHIRALCEL OD, *i*-PrOH-hexane, 1:99 v/v). In order to construct the tertiary methyl group, **5** was treated with dibromomethane and zinc in the presence of titanium tetrachloride[8] to give the diene **6**, $[\alpha]_D^{25}$ +90.6 (*c* 1.3, $CHCl_3$), in 81% yield. When the methylenation was carried out in prior to the desilylation, the *exo*-methylene product was obtained in a much poorer yield. Exposure of the hydroxy olefin **6** to *N*-bromosuccinimide (NBS)[9] in dichloromethane allowed chemoselective discrimination of two double bonds to give the single bromo-ether **7**, $[\alpha]_D^{27}$ +176.4 (*c* 1.3, $CHCl_3$), in 88% yield leaving the *exo*-methylene olefin. Hydrogenation of the *exo*-methylene **7** on Adams catalyst in methanol did not exhibit high convex-face diastereoselectivity which gave a mixture of *endo*- and *exo*-methyl isomers in 8:1 ratio. However, we were able to improve this less than satisfactory result by a fortuitous finding. Namely, when **7** was subjected to hydrogenation on 10% palladized carbon in dichloromethane, double bond migration instead of hydrogenation took place to generate the isomeric *endo*-olefin **8**. On hydrogenation in methanol in the presence of Adams catalyst, the *endo*-olefin **8** afforded diastereoselectively the *endo*-methyl product **9**, $[\alpha]_D^{31}$ +107.7 (*c* 0.9, $CHCl_3$), in an excellent yield (**Scheme 2**).



Scheme 2

Having introduced the requisite tertiary methyl group, the bromo-ether **9** was next treated with zinc in boiling ethanol containing acetic acid[9] so as to construct the quaternary center. The reaction proceeded readily as expected to give the secondary alcohol **10**, mp 87-88 °C, $[\alpha]_D^{28}$ –2.7 (*c* 1.3, $CHCl_3$), in 76% yield, which was oxidized with pyridinium dichromate (PDC) in dichloromethane to afford the ketone **11**, $[\alpha]_D^{30}$ –36.5 (*c* 0.5, $CHCl_3$). Grignard reaction of **11**, though cerium trichloride[9] was essential, proceeded diastereoselectively from the convex face to give the product **12**, $[\alpha]_D^{28}$ –3.1 (*c* 1.0, $CHCl_3$), having the requisite quaternary center in 77% yield. Thermolysis of the tertiary alcohol **12**, in boiling diphenyl ether (~260 °C) in the presence of

sodium hydrogen carbonate,[11] initiated a retro-Diels-Alder reaction with some decomposition to afford the cyclohexenol **13**, $[\alpha]_D^{28}$ +27.7 (*c* 0.3, $CHCl_3$), in 46% yield as a single isomer. On sequential ozonolysis and sodium borohydride reduction in the same flask, **13** furnished the triol **14**, by cleavage of the olefin bond, which was immediately transformed to the acetonide **15**, $[\alpha]_D^{28}$ –5.1 (*c* 0.7, $CHCl_3$), in 87% yield on reaction with 2,2-dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate (PPTS).[12] Oxidation of the primary hydroxyl group of **15** with PDC in DMF gave the carboxylic acid **16** which, on sequential acid treatments, furnished the target molecule (–)-malyngolide **1**, $[\alpha]_D^{28}$ –13.4 (*c* 0.3, $CHCl_3$) [natural[1]: $[\alpha]_D$ –13 (*c* 2, $CHCl_3$)], in 53% overall yield *via* the glycol **17** by deacetonization and lactonization[13] (**Scheme 3**).



Scheme 3

In summary, by exploiting the Rh(I)-(*R*)BINAP-catalyzed *meso*-asymmetrization and diastereoselective modification based on the stereochemical background of the chiral product obtained, a new tactic for diastereo- and enantiocontrolled construction of (–)-malyngolide **1** has been devised.

ACKNOWLEDGEMENTS

We are grateful to the Ministry of Education, Science, Sports and Culture, Japan, for financial support.

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13. Spectroscopic data of the representative intermediates: **8**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.71 (3H, s), 2.14 (2H, m), 2.31 (3H, m), 2.55 (1H, m), 2.89 (1H, m), 3.65 (1H, d, *J*=2.2 Hz), 4.17 (1H, m), 4.47 (1H, d, *J*=5.2 Hz), 5.42 (1H, m). **9**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.06 (3H, d, *J*=7.1 Hz), 1.38 (5H, m), 1.77 (1H, m), 1.93 (1H, m), 2.06 (1H, m), 2.12 (1H, m), 2.44 (1H, m), 2.87 (1H, m), 4.11 (1H, d, *J*=2.5 Hz), 4.19 (1H, m), 4.53 (1H, d, *J*=5.2 Hz), ^{13}C NMR ($CDCl_3$, 75 MHz) δ=20.4, 25.0, 28.0, 31.0, 35.2, 38.4, 42.2, 45.2, 48.9, 57.0, 76.9, 88.8. **10**: IR (film) ν=3266 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ=0.89 (3H, d, *J*=6.9 Hz), 0.97 (1H, ddd, *J*=3.6, 12.1, 12.1 Hz), 1.15 (1H, ddd, *J*=3.6, 12.1, 12.1 Hz), 1.27 (1H, d, *J*=8.0 Hz), 1.38 (1H, br s, exchangeable with D_2O), 1.45 (1H, dt, *J*=8.0, 1.7 Hz), 1.53 (1H, m), 1.75 (2H, m), 2.41 (1H, ddd, *J*=4.4, 5.2, 10.2 Hz), 2.60 (1H, ddd, *J*=3.6, 6.6, 10.2 Hz), 2.87 (1H, m), 2.97 (1H, m), 4.11 (1H, dt, *J*=12.1, 6.6 Hz), 6.09 (1H, dd, *J*=2.7, 5.8 Hz), 6.12 (1H, dd, *J*=2.7, 5.8 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=20.3, 26.6, 26.9, 27.1, 44.0, 44.5, 45.1, 45.3, 52.6, 68.4, 133.4, 133.6. **11**: IR (film) ν=1698 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ=1.11 (3H, d, *J*=6.9 Hz), 1.29 (1H, d, *J*=8.2 Hz), 1.39 (1H, dt, *J*=8.2, 2.2 Hz), 1.45 (2H, m), 2.10 (2H, m), 2.22 (1H, dt, *J*=17.3, 3.3 Hz), 2.65 (1H, ddd, *J*=3.0, 7.1, 9.3 Hz), 2.83 (1H, dd, *J*=4.4, 9.3 Hz), 3.03 (1H, m), 3.32 (1H, m), 6.06 (1H, dd, *J*=2.8, 5.5 Hz), 6.13 (1H, dd, *J*=2.8, 5.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=19.4, 26.7, 31.2, 40.4, 43.5, 45.2, 47.0, 49.8, 51.0, 135.5, 136.6, 214.1. **13**: IR (film) ν=3372 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz) δ=0.88 (3H, t, *J*=6.6 Hz), 1.01 (3H, d, *J*=7.1 Hz), 1.10-1.60 (18H, m), 1.69 (2H, m), 1.96 (1H, br s, exchangeable with D_2O), 2.07 (1H, m), 5.57 (1H, dd, *J*=1.4, 9.9 Hz), 5.64 (1H, dd, *J*=6.3, 9.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ=14.1, 21.2, 22.6, 23.6, 27.8, 29.3, 29.6, 30.2, 31.0, 31.9, 34.8, 42.5, 69.4, 132.0, 136.6.

(*Received in Japan* 9 *June* 1997; *revised* 20 *June* 1997; *accepted* 27 *June* 1997)