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A NEW ASYMMETRIC TOTAL SYNTHESIS OF ENANTIOPURE (–)-MALYNGOLIDE

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Abstract – A new asymmetric total synthesis of (–)-malyngolide is described. This synthesis is based on the originally developed catalytic asymmetric IMCP reaction; that is, α-diazo-β-keto sulfone (**13**) was successfully converted to cyclopropane (**12**) in 92 % yield with excellent enantioselectivity (97% ee), and cyclopropane (**12**) was successfully converted to (–)-malyngolide.

(–)-Malyngolide (Figure 1), isolated from the lipid extract of a shallow-water variety of *Lyngbya majuscula* from Kahala Beach, Oahu, in 1979, shows activity against *Mycobacterium smegmatis* and *Streptococcus pyogenes.*[1] (–)-Malyngolide possesses a δ-lactone incorporating two stereogenic centers, one of which is a quaternary carbon substituted with a nonyl-group side-chain and a hydroxymethyl group. Recently, structurally related (+)-tanikolide (Figure 1) was isolated from the lipid extract of a Madagascan collection of the marine cyanobacterium *Lyngbya majuscula*, exhibiting antifungal activity against *Candida albicans* and an LD_{50} of 3.6 μg/mL against brine shrimp and of 9.0 μg/mL against the snail.[2]

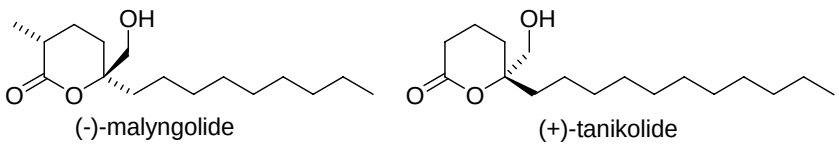


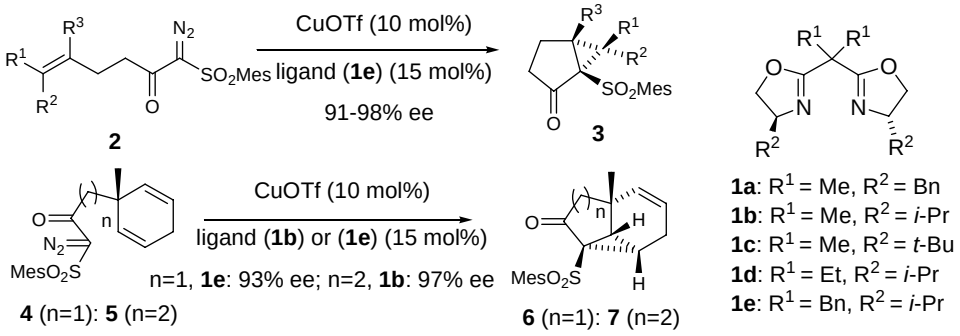
Figure 1 (–)-malyngolide and (+)-tanikolide

The interesting bioactivity of (–)-malyngolide and (+)-tanikolide combined with a challenging synthetic problem, that is, stereoselective construction of the tw[1]o stereogenic carbons including a quaternary carbon, has attracted considerable attention from many research groups addressing the total synthesis of

This paper is dedicated to the memory of the Emeritus Professor Kenji Koga of The University of Tokyo.

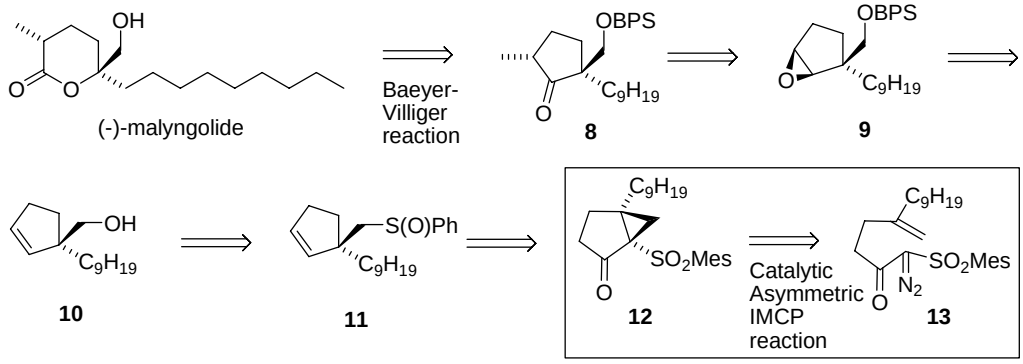
this rather small molecule.[3-6] We report herein a new asymmetric total synthesis of enantiopure (–)-malyngolide *via* a highly stereoselective approach.

We have reported the highly enantioselective catalytic asymmetric intramolecular cyclopropanation (IMCP) reactions of α-diazo-β-keto sulfones (Scheme 1).[7] In these reactions, **2**, **4**, and **5** are transformed to **3**, **6**, and **7**, respectively, with excellent enantioselectivity, ranging from 91 to 98 % ee. Since these products are highly crystalline and easily purified by a single recrystallization, this catalytic asymmetric IMCP reaction is useful for preparing new enantiopure building blocks for the efficient total synthesis of natural products. Recently, we have succeeded in the first asymmetric total synthesis of enantiopure (–)-allocyathin B_2 using the new enantiopure building block prepared by this IMCP reaction,[8] proving the usefulness of this asymmetric catalysis.



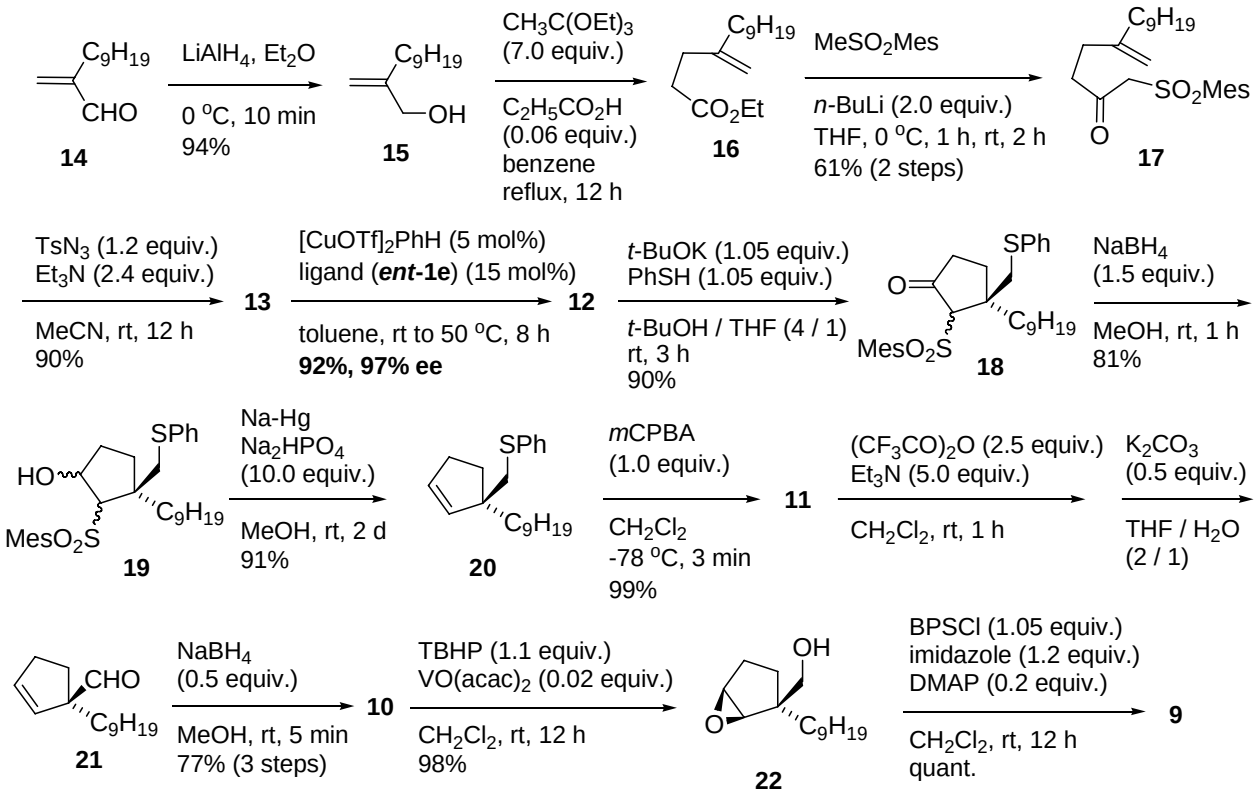
Scheme 1 Asymmetric catalysis on the intramolecular cyclopropanation reactions of α-diazo-β-keto sulfones

We envisioned that cyclopropane (**12**) would be a potential chiral building block for a new synthesis of (–)-malyngolide because the cyclopropane ring could open to afford the product with a stereogenic quaternary carbon required for the total synthesis of (–)-malyngolide. Our retosynthetic analysis of (–)-malyngolide is shown in Scheme 2.



Scheme 2 Retrosynthetic analysis of (–)-malyngolide

We decided to set an advanced intermediate (**9**) because **9** would be prepared from the corresponding homoallylic alcohol (**10**) *via* a stereoselective vanadium catalyzed epoxidation,[9] followed by successive protection with a BPS group, and the reaction of lithium dimethylcuprate with epoxide (**9**) was envisioned to occur from the less-hindered side to afford the corresponding alcohol, which would be oxidized to ketone (**8**), and which would be converted to (–)-malyngolide *via* Baeyer-Villiger reaction.[6] Alcohol (**10**) was expected to be obtained from the corresponding sulfoxide (**11**) *via* Pummerer rearrangement, followed by hydrolysis under basic conditions and successive reduction with $NaBH_4$. The requisite sulfoxide (**11**) could be obtained from the cyclopropane (**12**) by the ring-opening reaction with thiophenol under basic conditions,[8] followed by reduction of the resulting ketone, a reductive olefination using Na-Hg, and a chemoselective oxidation of the resulting sulfide. We surmised that the cyclopropane (**12**) would be prepared *via* the catalytic asymmetric IMCP reaction developed by our group;[7] hence, the substrate (**13**) was prepared first.



Scheme 3 Synthesis of enantiopure **9** *via* catalytic asymmetric IMCP reaction

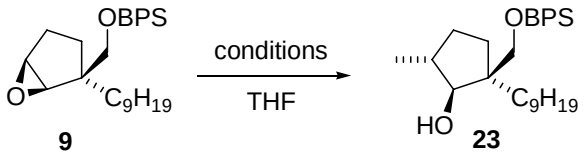
As shown in Scheme 3, aldehyde (**14**)[10] was reduced to **15** with $LiAlH_4$ (94%), which was transformed to **16** *via* the Johnson ortho ester rearrangement,[11] followed by a reaction with a dianion of mesitylmethylsulfone to produce **17** in 61% yield (2 steps). **17** was successfully converted to

α-diazo-β-keto sulfone (**13**) (90%) by the conventional method using tosylazide and triethylamine to set the stage for the catalytic asymmetric IMCP reaction.

The catalytic asymmetric IMCP reaction of **13** was carried out under the conditions already reported.[7] The intramolecular cyclopropanation of **13** with the *in-situ* prepared asymmetric catalyst mixing $[CuOTf]_2 \cdot C_6H_6$ (5 mol %; 10 mol % as CuOTf) and ligand (***ent*-1e**) (15 mol %) successfully afforded **12**[12] in 92% yield with excellent enantioselectivity (97% ee). Gratifyingly, **12** was purified by recrystallization to be optically pure. At this point the absolute configuration of **12** was expected as described in Scheme 2; its realization was determined by comparing the sign of the specific rotation of the synthesized malyngolide with that of (–)-malyngolide because **12** was not suitable for the X-Ray crystallographic analysis.

The reaction of **12** with potassium thiophenoxide, prepared by thiophenol and potassium *tert*-butoxide, successfully opened the cyclopropane ring to produce the sulfide (**18**) (90%), which was reduced to alcohol (**19**) with $NaBH_4$ (81%). Reductive alkenylation by treating β-hydroxy sulfone (**19**) with Na-Hg in methanol cleanly generated the corresponding alkene (**20**) (91%), which was selectively converted to sulfoxide (**11**) by a careful oxidation using *m*CPBA (99%) at low temperature (–78 °C). Pummerer rearrangement of **11**, and the following hydrolysis under basic conditions generated aldehyde (**21**), which was reduced to homoallylic alcohol (**10**)[13] with $NaBH_4$ (77%, 3 steps). The stereoselective vanadium catalyzed epoxidation of **10** under Sharpless's conditions[9] generated **22** as a sole product (98%), whose silyl ether (**9**)[14] was subjected to the epoxide-opening reaction with lithium dimethylcuprate.

Table 1. Epoxide-opening reaction with Me_2CuLi

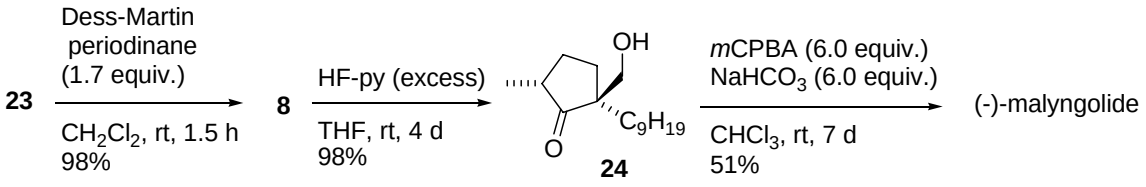


9 **23**

Entry	Reagents	Additive	Temp (ºC)	Time (h)	Yield (%)[a]
1	Me_2CuLi (3.0 equiv.)	–	-20	2	0
2	Me_2CuLi (3.0 equiv.)	$BF_3 \cdot OEt_2$ (1.0 equiv.)	-78	12	78

[a]Isolated yield.

As shown in Table 1, no product formed in the reaction of **9** with lithium dimethylcuprate; however, use of one equivalent of $BF_3 \cdot OEt_2$[15] as an additive dramatically incited the epoxide to react with lithium dimethylcuprate from the less-hidered side, generating the desired product (**23**) as a sole product in 78% yield even at –78 ºC.



Scheme 4 Asymmetric total synthesis of enantiopure (–)-malyngolide

Dess-Martin periodinane oxidized **23** to ketone (**8**) (98%),[16] which was desilylated with *n*-Bu_4NF to afford (**24**) in 61% yield along with forming its C-5 epimer in 34% yield; however, use of excess HF·py gratifyingly gave only (**8**) in 98% yield. While the Baeyer-Villiger reaction of (**24**) required rather long time (7 days) to furnish the product in a reasonable yield (51%), the obtained product proved to be identical in all respects to the reported spectral data (^{1}H-NMR, IR, MS, and ^{13}C-NMR spectra and $[\alpha]_D$)[1] of malyngolide, and the specific rotation ($[\alpha]_D^{21}$) showed –13.0º (c 0.7, $CHCl_3$), revealing that (–)-malyngolide had been synthesized. At the same time, this result disclosed that cyclopropane (**12**) possesses 1*S* configuration, indicating that the enantioselectivity of the catalytic asymmetric IMCP reaction of **13** is in consistent with those observed in the reactions of **2** ($R^1 = R^2 = R^3 = H$), and outcome of this enantioselectivity is well explained by our proposed model.[7]

In summary, a new asymmetric total synthesis of enantiopure (–)-malyngolide was achieved. This synthesis is based on the originally developed catalytic asymmetric IMCP reaction; that is, α-diazo-β-keto sulfone (**13**) was successfully converted to cyclopropane (**12**) in 92 % yield with excellent enantioselectivity (97% ee). Since cyclopropane (**12**) was crystalline, **12** was purified by recrystallization to be optically pure, ensuring that (–)-malyngolide and all the chiral products prepared are enantiomerically pure. This synthesis would be applicable to the asymmetric total synthesis of enantiopure (+)-tanikolide because the formation of ***ent-12*** is expected in the catalytic asymmetric IMCP reaction using ligand (**1e**); further studies will be reported in due course.

ACKNOWLEDGEMENTS

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12. **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.95 (2H, s), 2.65 (6H, s), 2.38(1H, d , J = 5.3 Hz), 2.30 (3H, s), 2.26–2.01 (4H, m), 1.80 (1H, d , J = 5.3 Hz), 1.41–1.28 (16H, m), 0.89 (3H, t , J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 204.4, 142.9, 140.3, 135.5, 131.9, 58.7, 46.1, 35.4, 33.6, 32.4, 32.0, 29.6, 29.4, 29.0, 27.1, 26.0, 23.3, 22.9, 21.0, 18.8, 14.2; IR (neat) ν_{max} 3855, 3651, 2927, 1733, 1459, 1309, 1141 cm^{-1}; FAB-MS $[M+H]^+$ calculated for $C_{24}H_{37}O_3S_1$: 405.2463, found : 405.2476; $[\alpha]_D^{26}$ +123.7 º (*c* 1.0, $CHCl_3$); mp 73 ºC (hexane).
13. **10**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84 (1H, ddd, J = 5.6, 2.2, 2.2 Hz), 5.43 (1H, ddd, J = 5.6, 2.4, 2.0 Hz), 3.46 (1H, d, J = 10.4 Hz), 3.41 (1H, d, J = 10.4 Hz) 2.37–2.33 (2H, m), 1.86–1.79 (1H, m), 1.69–1.62 (1H, m), 1.56 (1H, s), 1.37 (2H, m), 1.25–1.19 (14H, m), 0.88 (3H, t, J = 4.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.9, 132.7, 69.4, 55.0, 36.7, 32.6, 31.9, 31.0, 31.0, 30.5, 29.7, 29.4, 24.6, 22.7, 14.1; IR (neat) ν_{max} 3844, 2928, 2856, 2336, 1038, 742, 726 cm^{-1}; FAB-MS $[M–H]^+$ calculated for $C_{15}H_{27}O$: 223.2062, found : 223.2060; $[\alpha]_D^{25}$ –13.5 º (*c* 1.7, $CHCl_3$).
14. **9**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (1H, d, J = 9.6 Hz), 3.52 (1H, d, J = 9.6 Hz), 3.47 (1H, m), 3.35 (1H, d, J = 2.7 Hz), 1.95 (1H, dd, J = 8.3, 4.2 Hz), 1.70–1.57 (2H, m), 1.42–1.10 (17H, m), 1.07 (9H, s), 0.88 (3H, t, J = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.6, 135.5, 129.5, 127.5, 66.2, 61.8, 57.6, 47.5, 32.0, 31.6, 30.6, 29.7, 29.7, 29.4, 26.9, 26.7, 26.4, 23.9, 22.8, 19.5, 14.2; IR (neat) ν_{max}

3136, 3076, 3052, 3028, 2932, 2800, 2740, 2364, 1592, 1560, 1490, 1472, 1458, 1428, 1380, 1114, 1094, 824, 740, 702, 610 cm^{-1}; FAB-MS $[M–H]^+$ calculated for $C_{31}H_{45}O_2Si$: 477.3189, found : 477.3199; $[\alpha]_D^{23}$ +20.9 º (*c* 1.0, $CHCl_3$).

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16. **8**: ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.59 (4H, m), 7.42–7.34 (6H, m), 3.75 (1H, d, *J* = 8.2 Hz), 3.40 (1H, d, *J* = 8.2 Hz), 2.32–2.16 (2H, m), 1.84 (1H, dd, *J* = 7.2, 5.3 Hz), 1.47–1.41 (1H, m), 1.41–1.15 (17H, m), 1.11 (3H, d, *J* = 5.7 Hz), 1.00 (9H, s), 0.86 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.9, 135.6, 135.5, 129.5, 127.6, 68.0, 54.3, 45.3, 33.9, 31.9, 30.4, 29.5, 29.4, 29.3, 28.7, 28.3, 26.8, 24.5, 22.7, 19.3, 14.3, 14.1; IR (neat) ν_{max} 3072, 3052, 2932, 2860, 2740, 2336, 1738, 1592, 1458, 1428, 1114, 1092, 824, 702, 614 cm^{-1}; FAB-MS $[M–H]^+$ calculated for $C_{32}H_{47}O_2Si$: 493.3345, found : 493.3343; $[\alpha]_D^{23}$ –25.3 º (*c* 1.0, $CHCl_3$).