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Optimization of ring-contraction of the *meso* enedione epoxide for chiral building block synthesis

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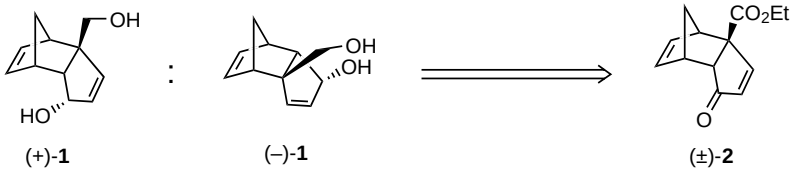
Abstract—The ring-contraction of the enedione epoxide obtained from the adduct of benzoquinone and cyclopentadiene is mainly affected by the amount of base used. Excellent yields (>80%) of the ring-contracted product were consistently obtained when the epoxide was treated with a 0.5 equiv. of ethanolic sodium hydroxide in ethanol. The versatility of the chiral building block accessible from the ring-contracted product has also been demonstrated by an alternative diastereocontrolled synthesis of (+)-tanikolide, a toxic and antifungal marine natural product isolated from *Lyngbya majuscula*. © 2002 Published by Elsevier Science Ltd.

We have developed[1] a chiral production of the tricyclic diol **1** in both enantiomeric forms by employing lipase-mediated resolution of the racemic precursor (±)-**1** obtained from the known tricyclic keto-ester (±)-**2**[2] (Scheme 1). Owing to its sterically biased framework allowing convex-face selective modification and its thermal lability to generate a cyclopentene double bond with extrusion of a cyclopentadiene molecule, the diol **1** was used as a synthetic equivalent of a functionalized chiral cyclopentadienol. It allowed the efficient preparation of a naturally occurring antiviral carbocyclic nucleoside (–)-neplanocin[3] and two monoterpenes, (–)-iridolactone[4] and (+)-pedicularis-lactone,[4] in an enantio- and diastereocontrolled manner due to its inherent steric and chemical nature. Although the keto-ester (±)-**2** was easily formed from the *meso*-enedione epoxide **3**, generated from the Diels–Alder adduct between benzoquinone and cyclopentadiene, by a Favorskii-type ring-contraction as originally reported by Herz and co-workers,[2] the reaction was very capricious, affording the ring-contracted product (±)-**2** in a range of yields which made the consistent production of the chiral building block very difficult. We therefore, sought optimal conditions for the ring-contraction of the enedione epoxide **3** to achieve the consistent production of the chiral building block **1** and thereby widen its utilization in the enantioselective construction of a variety of chiral materials. We report here good conditions for the satisfactory production of the keto-ester (±)-**2** and its transformation into both of the enantiomeric diols **1** in an enantiopure state, one of which has never been obtained in a pure state at this stage before.[1] The use of the enantiopure product (–)-**1** for an alternative synthesis of (+)-tanikolide,[5,6] a toxic and antifungal marine natural product isolated from *Lyngbya majuscula*, was also described to demonstrate the versatility of the chiral building block.

Based on the procedure by Herz and co-workers,[2] we examined the reaction extensively using sodium hydroxide in ethanol as well as sodium ethoxide in ethanol and sodium methoxide in methanol. As shown, it was found that sodium hydroxide was superior to the others and that the amount of the base was the most important



(+)-**1** : (–)-**1** ⟹ (±)-**2**

Scheme 1.

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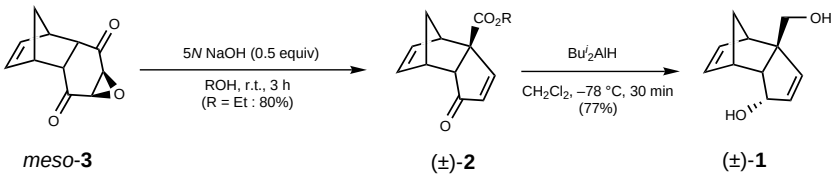


Scheme 2.

carried out in the presence of 0.5 equiv. of sodium hydroxide, the ring-contracted product (±)-**2** was obtained cleanly in good yield. Thus, stirring the epoxide **3** (19.0 g, 100 mmol) in EtOH (480 ml) with 20% ethanolic NaOH (10 ml, 50 mmol) at room temperature for 3 h afforded the keto-ester (+)-**2** (17.4 g, 80%) after the standard work-up and purification by silica gel column chromatography. Reduction of the product **2** using lithium aluminum hydride afforded the desired diol (±)-**1**, but was accompanied by a considerable amount of by-products presumably due to a concurrent [3,3]-sigmatropic rearrangement under these conditions.[1,7] However, the reduction of the keto-ester (±)-**2** using diisobutylaluminum hydride (DIBAL) at –78°C in dichloromethane[1] allowed the desired reduction to give the crystalline diol (±)-**1**, mp 122–124°C, in satisfactory yield (Scheme 2).

Resolution of the racemic diol (±)-**1** (5.0 g, 28.2 mmol) was carried out in ether (240 ml) containing vinyl acetate (3.9 ml, 42 mmol) in the presence of immobilized lipase (Lipase LIP, Toyobo, 1.25 g) at ~30°C for 3.5 h to give the diacetate (–)-**4**, $[\alpha]_D^{26}$ –112.2 (*c* 1.2, $CHCl_3$) (95% ee),[8] (3.18 g, 43%) and the monoacetate (+)-**5**, $[\alpha]_D^{26}$ +133.9 (*c* 1.0, $CHCl_3$) (>99% ee),[8] (2.73 g, 44%) after silica gel column chromatography. The diacetate (–)-**4** gave the enantiopure diol (–)-**1**,[8] mp 136–138°C, $[\alpha]_D^{27}$ –187.0 (*c* 0.4, EtOH),[6] in 78% yield after methanolysis with potassium carbonate followed by recrystallization of the optically enriched diol (–)-**1** from MeOH–$CHCl_3$. Alkaline methanolysis of the monoacetate (+)-**5** afforded the enantiopure diol (+)-**1**,[8] mp 134–136°C, $[\alpha]_D^{26}$ +175.1 (*c* 1.0, EtOH), quantitatively (Scheme 3).

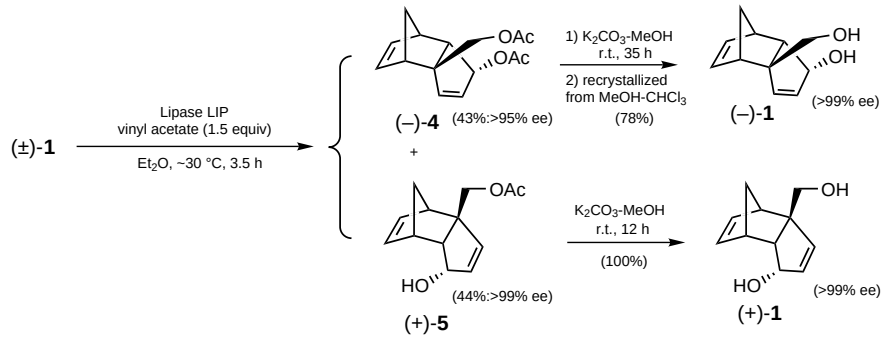
To demonstrate the capability of the diol **1** for constructing a quaternary stereogenic center in a diastereocontrolled manner, we conducted an alternative synthesis of (+)-tanikolide **20** the absolute structure of which was recently established unambiguously by our laboratory[6] through an enantiocontrolled procedure employing the catalytic asymmetric synthesis.[9,10] Thus, the diol (–)-**1** was oxidized chemoselectively using manganese(IV) oxide to give the keto-alcohol **6**, $[\alpha]_D^{26}$ –15.9 (*c* 1.0, $CHCl_3$), quantitatively. After benzylation, the resulting benzyl ether **7**, $[\alpha]_D^{22}$ –61.8 (*c* 0.9, $CHCl_3$), was treated with 30% hydrogen peroxide in methanol containing 1N NaOH to give the *exo*-epoxide **8** which, on reflux with lithium aluminum hydride in dioxane, afforded the single diol **9**, $[\alpha]_D^{21}$ –14.9 (*c* 1.0, $CHCl_3$), by concurrent diastereoselective selective reduction of the ketone functionality and regioselective cleavage of the epoxide ring. To differentiate the two secondary hydroxy functionalities in the molecule, the diol **9** was treated with *N*-bromosuccinimide (NBS) to form the bromo-ether **10**, $[\alpha]_D^{24}$ –58.4 (*c* 1.4, $CHCl_3$), leaving the *exo*-hydroxy functionality intact. After protection of the *exo*-hydroxy functionality as the MOM–ether **11**, $[\alpha]_D^{24}$ +6.9 (*c* 1.5, $CHCl_3$), the bromo-ether functionality was cleaved reductively with zinc and acetic acid in methanol to liberate the *endo*-hydroxy functionality to give rise to the *endo*-alcohol **12**, $[\alpha]_D^{22}$ +21.1 (*c* 1.1, $CHCl_3$). The overall yield of **12** from the starting diol (–)-**1** was 46% in seven steps (Scheme 4).

To construct the quaternary stereogenic center required for the target molecule **20**, the *endo*-alcohol **12** was refluxed with 4 equiv. of *N*,*N*-dimethylacetamide dimethyl acetal[11] in diphenyl ether. Under these conditions, we expected that a concurrent retro-Diels–Alder reaction, ketene aminoacetal formation and an Eschenmoser rearrangement would occur to generate the cyclopentene **14** having the requisite quaternary center presumably via the transient monocyclic intermediate **13**. The expected reaction did indeed take place within 60 min to furnish the cyclopentene **14**, $[\alpha]_D^{24}$ +35.7 (*c* 1.5, $CHCl_3$), in 63% yield. Transformation of the product **14** into the target molecule (+)-tanikolide **20** was carried out in a straightforward manner. Thus, the tertiary amide functionality of **14** was reduced with lithium triethylborohydride[12] to give the primary alcohol **15**, $[\alpha]_D^{23}$ +41.9 (*c* 0.6, $CHCl_3$), which was converted into the inseparable diene mixture **17** ($E/Z = 1{:}10$ by ^{1}H NMR) via the aldehyde **16** by sequential pyridinium dichromate (PDC) oxidation, Wittig reaction and MOM-deprotection.[13] The resulting mixture **17** was oxidized to the cyclopentenone mixture **18** which, on catalytic hydrogenation over palladium on charcoal in ethanol containing chloroform,[14] afforded the single keto-alcohol **19**, $[\alpha]_D^{25}$ –8.1 (*c* 1.0, $CHCl_3$), by concurrent hydrogenation and hydrogenolysis. Finally, Baeyer–Vil-

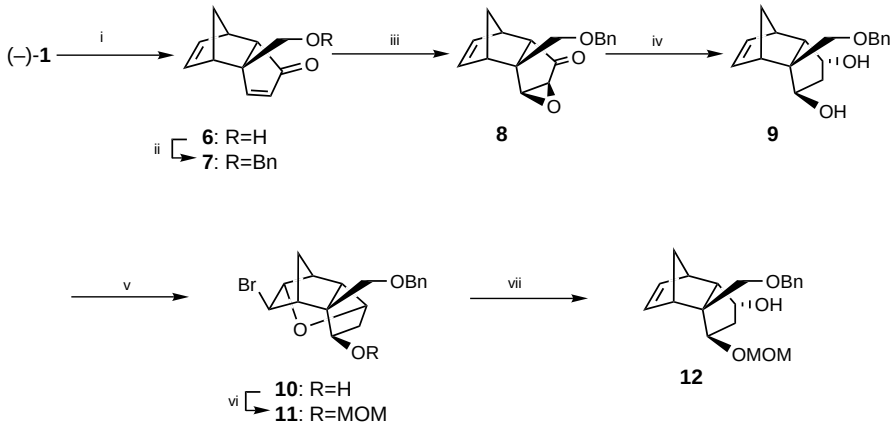
Table 1. Ring-contraction reaction[a] of the *meso*-enedione epoxide **3**

Entry	Base (equiv.)	Solvent	Product (R) (%)[b,c]
1	NaOEt (1.0)	EtOH	Et: 29
2	NaOMe (1.0)	MeOH	Me: 32
3	NaOH (1.0)	EtOH	Et: 61[d]
4	NaOH (0.7)	EtOH	Et: 75[d]
5	NaOH (0.5)	EtOH	Et: 80[d]
6	NaOH (0.3)	EtOH	Et: 62[d]

[a] All reactions were carried out at room temperature.
[b] Isolated yield after silica gel column chromatography.
[c] Virtually, no starting material was recovered.
[d] None of the hydrolysis products from **3** and **1** was isolated.



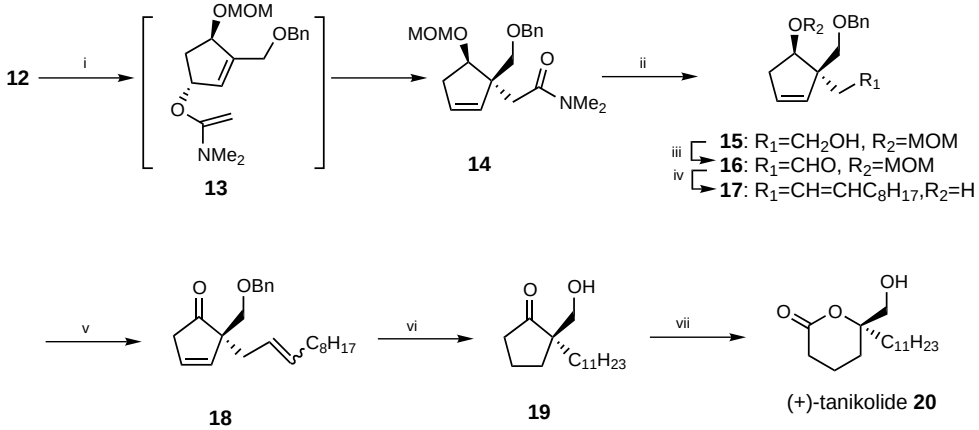
Scheme 3.



Scheme 4. *Reagents and conditions*: (i) MnO_2, CH_2Cl_2, rt (100%); (ii) Bn–Br, Bu_4NHSO_4 (cat.), 50% NaOH, benzene (80%); (iii) 30% H_2O_2, 1N NaOH, MeOH rt; (iv) $LiAlH_4$, dioxane, reflux (70%, two steps); (v) NBS, CH_2Cl_2, rt (86%); (vi) Zn, AcOH–MeOH (1:10), reflux (95%).

liger oxidation of the keto-alcohol **19** was carried out under the conditions using *m*-chloroperbenzoic acid in the presence of triflic acid[15] to give (+)-tanikolide **20**, mp 39–41°C, $[\alpha]_D^{25}$ +3.0 (*c* 0.8, $CHCl_3$){natural:[5] $[\alpha]_D^{25}$ +2.3 (*c* 0.7, $CHCl_3$); synthetic:[6] mp 38–40°C, $[\alpha]_D^{25}$ +2.9 (*c* 0.65, $CHCl_3$)}, which was identical with an authentic sample in all respects. The overall yield of (+)-tanikolide **20** from the tricyclic alcohol **12** was 30% in seven steps; therefore, the total yield from the chiral building block (–)-**1** was 14% in fourteen steps (Scheme 5).

In conclusion, we have found that the optimal conditions for the ring-contraction of the enedione epoxide obtained from the adduct of benzoquinone and cyclopentadiene gave the tricyclic keto-ester, which



Scheme 5. *Reagents and conditions*: (i) $MeC(NMe_2)(OMe)_2$, Ph_2O, reflux (63%); (ii) $LiEt_3BH$, THF (99%); (iii) PDC, CH_2Cl_2, rt; (iv) $C_9H_{19}PPh_3I$, NaHMDS, THF, then satd HCl–MeOH (72%, two steps); (v) PCC, CH_2Cl_2 (95%). (vi) H_2, 10% Pd–C (cat.), EtOH–$CHCl_3$ (3:1) (83%); (vii) *m*-CPBA, TfOH (cat.), CH_2Cl_2 (85%).

served as the precursor of the versatile cyclopentenol chiral building block, in satisfactory yield. The versatility of the chiral building block has also been demonstrated by an alternative diastereocontrolled synthesis of (+)-tanikolide, a toxic and antifungal marine natural product isolated from *Lyngbya majuscula*.

Acknowledgements

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