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Diastereotopic Group Selective Intramolecular Conjugate Addition of 4-(2-Hydroxyethyl)-*p*-Quinol Derivatives: Synthesis of the Optically Pure *cis*-7-Oxabicyclo[4.3.0]non-2-en-4-one Skeleton

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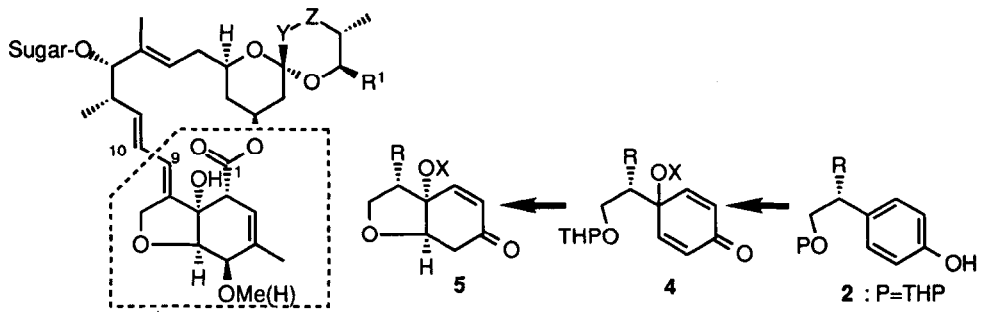
Abstract: Diastereotopic group selective cyclization of 4-(2-hydroxyethyl)-*p*-quinol derivatives was achieved and the reaction applied to the synthesis of the optically pure *cis*-7-oxabicyclo[4.3.0]non-2-en-4-one skeleton.

Asymmetric synthesis based on the dissymmetrization of symmetric compounds, such as the meso compounds and compounds having a prochiral carbon atom, is one of the most powerful ways to get optically pure substrates, and many methodologies have been developed so far.[1]

During our studies directed toward the synthesis of optically active avermectins **1** having extremely potent anthelmintic and insecticidal activity,[2,3,4] we examined the asymmetric synthesis of the optically pure oxabicyclic compound **5**, which is proposed as a useful intermediate to the hexahydrobenzofuran portion (C1-C9 unit) of **1**. The reaction consists of asymmetric tetrahydrofuran ring formation by dissymmetrization of the prochiral center with two identical functional groups of the quinol derivatives **4** having the stereogenic center on the side-chain. We succeeded in diastereotopic group selective cyclization and the synthesis of optically pure **5** (Scheme 1).



1 R^1 : s-Bu, i-Pr;
Y-Z : CH=CH, $CH_2CH(OH)$

Scheme 1

In the first place, photooxidation and reductive workup of racemic **2** (R=Me, P=H)[5] by a previous reported procedure[6] were carried out to give directly the cyclized products **5** (R=Me, X=H) and **6** (R=Me, X=H). However, both the chemical yield and diastereoselectivity were unsatisfactory.[7] A stepwise method was next studied using racemic compounds **3** and **4** with a methyl, methoxymethyl, or benzyloxymethyl substituent (Table).[5] Quinols **3** were prepared by photooxidation and reductive workup of phenols **2** (P=THP) in good yields (R=Me, 75%; R=CH_2OMe, 76%; CH_2OBn, 76%).[8] Acid treatment (90% AcOH aq., 50°C) of **3** afforded the cyclized products **5** (X=H) and **6** (X=H) in high yields, but no diastereoselectivity (**5**/**6**=1/1~1.4/1) was

observed (entries 1, 5, and 8). However, the use of the ester derivatives **4** (X=acyl),[9] obtained by acylation of **3**, gave better selectivities (entries 2-4, 6-7 and 9,10). In these cases, the bulkiness of the alkyl substituent had little influence and the benzoyl function was the best choice among the acyl groups studied. The relative stereochemistries of the products in entry 10 were determined by X-ray structure analysis of compound **7** obtained by hydrogenation and hydrogenolysis of **5** (R=CH_2OBn, X=Bz) (Scheme 2). The stereochemistries of the other products were tentatively assigned by assuming the same stereochemical course.

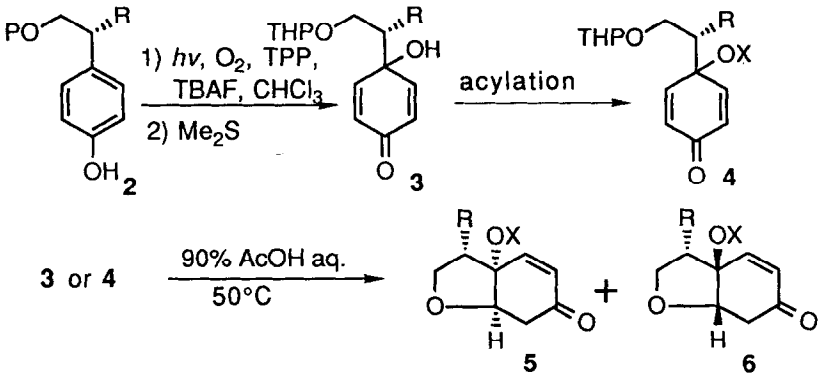
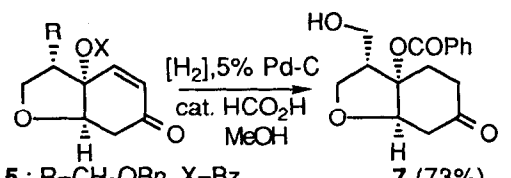


Table. Acid treatment of quinol derivatives (**3** and **4**)

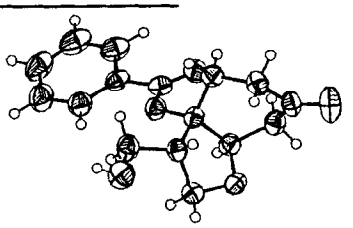
Entry	Substrate (**3**, **4**)		Yield (%)	Ratio(**5** : **6**)[a]
1	**3** R=Me		93	1 : 1
2	**4** R=Me	X=Ac	94	4 : 1
3		X=i-PrCO	86	4.1 : 1
4		X=Bz	93	**4.6 : 1**
5	**3** R=CH_2OMe		95	1 : 1
6	**4** R=CH_2OMe	X=Ac	87	3.6 : 1
7		X=Bz	99	**4 : 1**
8	**3** R=CH_2OBn		98	1.4 : 1
9	**4** R=CH_2OBn	X=Ac	96	3 : 1
10		X=Bz	99	**4.5 : 1**

a) Determined by ^{1}H-NMR spectroscopy



5 : R=CH_2OBn, X=Bz **7** (73%)

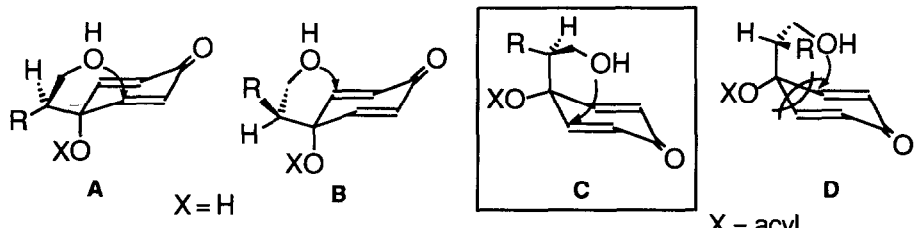
Scheme 2



X-Ray crystallographic structure of **7**

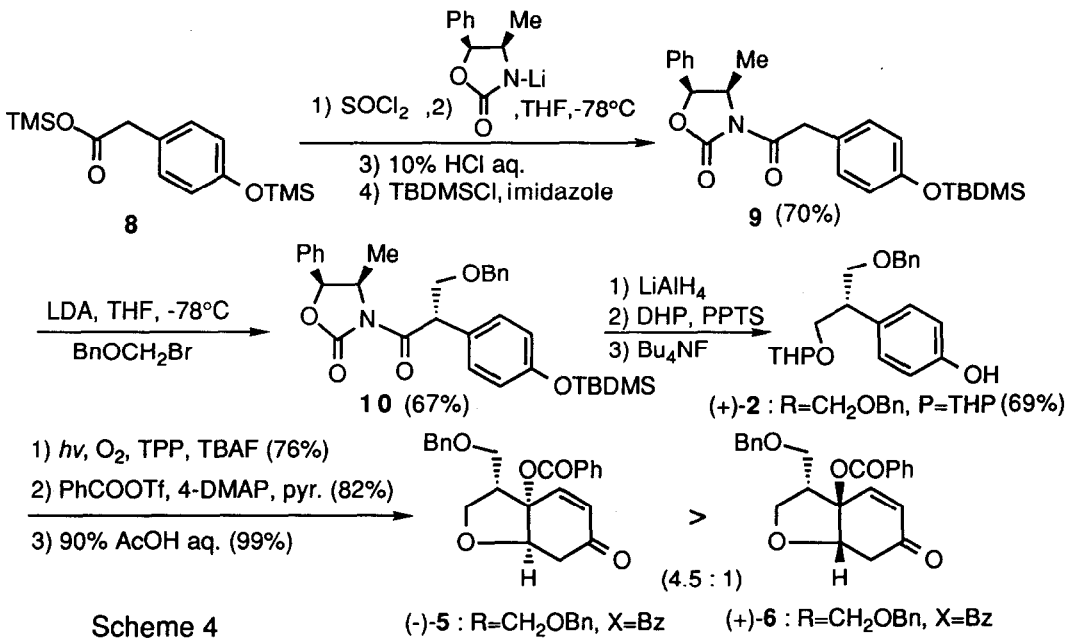
The diastereotopic group selective intramolecular 1,4-conjugate addition observed in acylated compounds **4** might be rationalized as follows. Among the four transition states (**A-D**) proposed for the cyclization process, acylated compounds **4** would exist as conformers **C** and **D**, where the bulky ester group occupies the equatorial

position. Conformer **C** then predominated over conformer **D** because of the repulsion between the ring and the substituent of the side-chain in conformer **D** (Scheme 3).



Scheme 3

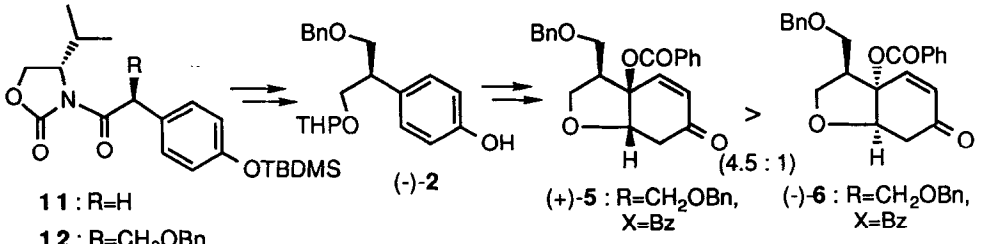
Having achieved the diastereoselective cyclization in the racemic series, the synthesis of optically pure **2** and its asymmetric cyclization were next studied (Scheme 4). As an alkyl substituent (R), the benzyloxymethyl group was selected for its easy transformation. Diastereoselective alkylation of the imide **9**, synthesized from the oxazolidinone of (1*S*,2*R*)-norephedrine and **8**[10], afforded **10** (>99% de),[11, 12] which was converted to (+)-**2** ([α]$_D$ +6.7) by reduction with $LiAlH_4$, protection of the primary alcohol, and desilylation. Photooxidation of (+)-**2** followed by benzoylation and acid treatment gave (-)-**5** (R=CH_2OBn, X=Bz) ([α]$_D$ -99.6) and its diasteromer (+)-**6** (R=CH_2OBn, X=Bz) ([α]$_D$ +159) in a ratio of 4.5 to 1. The absolute configuration was deduced from the consideration of the stereochemistry during alkylation of the chiral imide **9**[12] and determined unambiguously by a CD study [(-)-**5** (R=CH_2OBn, X=Bz): CD λ_{ext} (nm)(Δε) 240 (-30.0), 220 (+8.2); (+)-**6** (R=CH_2OBn, X=Bz): CD λ_{ext} (nm)(Δε) 235 (+41.4), 215 (-0.6)].[13]



Scheme 4

The enantiomer of (-)-**5** (R=CH_2OBn, X=Bz), (+)-**5** (R=CH_2OBn, X=Bz) could also synthesized by the same procedure as (-)-**5** (R=CH_2OBn, X=Bz) except for the chiral auxiliary. The imide **11** was synthesized from **8** and the oxazolidinone derived from (*S*)-(+)-valinol similar to **9** in 60% yield. The benzyloxymethylation

of **11** afforded **12** in 73% yield (>99% de).[12] Conversion of **12** to (-)-**2** was done in a three step sequence (83% overall yield). The subsequent yields and the diastereoselectivity for the formation of (+)-**5** and (-)-**6** were the same as those shown in Scheme 4 (Scheme 5).



Scheme 5

In conclusion, we clarified the factors affecting the favorable selectivity in an intramolecular conjugate addition of 4-(2-hydroxyethyl)-*p*-quinol derivatives and developed a new method for obtaining the optically pure oxabicyclic compounds such as (-)-**5**, having the same absolute stereochemistry as the hexahydrobenzofuran portion of avermectines **1**, and its enantiomer, (+)-**5**. The compounds **5** still have the enone unit and would promise to be useful intermediates for the optically pure compounds.

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4. (a) For total synthesis, see: A. Armstrong and S. V. Ley, *Synlett.*, **1990**, 323 and references cited therein. (b) For recent synthetic studies of the hexahydrobenzofuran portion of **1**, see:M. Hirama, T. Noda, S. Ito, and C. Kabuto, J. *Org. Chem.*, **53**, 706 (1988). M. E. Jung and V. C. Truc, *Tetrahedron Lett.*, **29**, 6059 (1988). A. G. M. Barrett, T. E. Barta, and J. A. Flygare, M. Sabat, and C. D. Spilling, *J. Org. Chem.*, **55**, 2409 (1990). P. J. Parsons, P. Willis, and S. C. Eyley, *Tetrahedron*, **48**, 9461 (1992). S. Fujiwara and A. B. Smith, III, *Tetrahedron Lett.*, **33**, 1185 (1992) and references cited therein.
5. Racemic compounds were used and one enantiomer is depicted. Details of these syntheses will be published elsewhere.
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7. The total chemical yields of **5** and **6** are 36% at pH 9 and 35% at pH 7 and diastereoselecticity of **5** and **6** is 1/1~1/2.
8. For photooxidation reaction, see W. Adam and P. Lupón, *Chem. Ber.*, **121**, 21 (1988) and H. H. Wasserman and J. E. Pickett., *Tetrahedron Lett.*, **41**, 2155 (1985).
9. Usual acylation condition (corresponding acid anhydride, 4-DMAP, pyr.) was used; **4** (R=Me: X=Ac, 91%; X=i-PrCO, 100%; X=Bz, 93%), **4** (R=CH_2OMe: X=Ac, 99%; X=Bz, 70 %), **4** (R=CH_2OBn: X=Ac, 88%; X=Bz, 82 %. In this case, PhCOOTf was used in place of $(PhCO)_2O$).
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