A concise enantio- and diastereo-controlled synthesis of (−)-quinic acid and (−)-shikimic acid

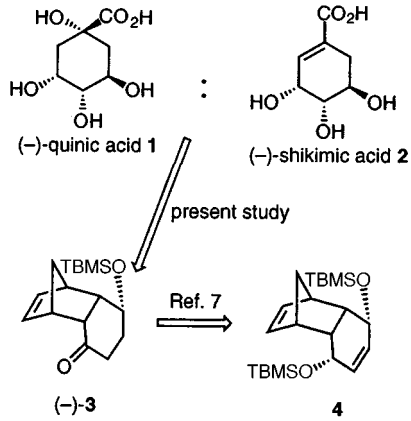
Kou Hiroya and Kunio Ogasawara*†

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-8578: Japan

(−)-Quinic acid and (−)-shikimic acid, both recognized as the key intermediates in the shikimate pathway in plants and microorganisms, have been synthesized concisely in an enantio- and diastereo-controlled manner starting from a synthetic equivalent of (*R*)-4-hydroxycyclohex-2-enone.

Both (−)-quinic acid **1** and (−)-shikimic acid **2** occur widely in both plants and microorganisms in which they have been recognized as the pivotal biogenetic precursors in the biosynthesis of a variety of aromatic natural products in the biogenetic pathway known as the shikimate pathway.[1] Since the shikimate pathway is only operative in plants and microorganisms, development of a flexible synthetic procedure for both (−)-quinic acid **1** and (−)-shikimic acid **2** as well as a variety of their derivatives is of great importance in biogenetic studies as well as in the search for herbicidal, antifungal or antibacterial agents that do not affect mammals.[1,2] Although a number of procedures including enantiocontrolled approaches have been developed for the construction of (−)-shikimic acid[3,4] **2**, only three racemic[5] and one chiral[6] procedures have been reported for the synthesis of (−)-quinic acid **1** to date. To explore a unified enantiocontrolled route to both (−)-quinic acid **1** and (−)-shikimic acid **2**, we selected the enantiomerically pure tricyclic ketol silyl ether[7] **3**, obtained from the catalytic asymmetrization[7,8] of the *meso* tricyclic ene-1,4-diol bis-silyl ether **4** and which serves as a synthetic equivalent of (*R*)-4-hydroxycyclohex-2-enone,[9] as the starting material. We describe here a diastereoselective conversion of (−)-**3** into both (−)-quinic acid **1** and (−)-shikimic acid **2** in a concise manner in good overall yields (Scheme 1).

Ketol silyl ether[7,8] (−)-**3** (>99% ee) was treated with $OC(OMe)_2$ in THF in the presence of NaH to afford in good yield the β-keto ester which existed in the single enol form‡ **5**, $[\alpha]_D^{29}$ −191.0 (*c* 1.71, $CHCl_3$). On hydroxylation in DMSO containing KF and $P(OEt)_3$,[10,11] the enol **5** gave diastereoselectively the α-hydroxy-β-keto ester **6**, $[\alpha]_D^{30}$ −59.8 (*c* 1.09, $CHCl_3$), as a single stereoisomer. As expected, NOE experiments indicated the *exo*-stereochemistry of the hydroxy functionality, which was confirmed by the later conversion.

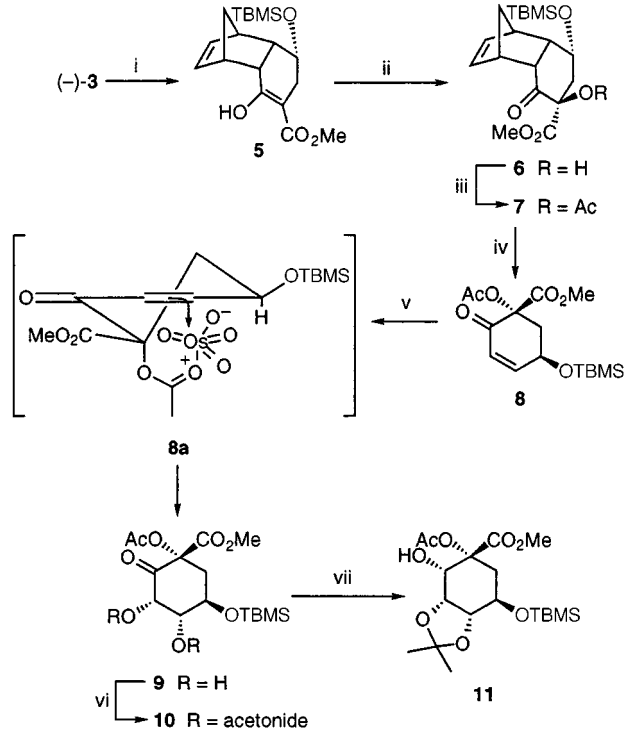


Scheme 1

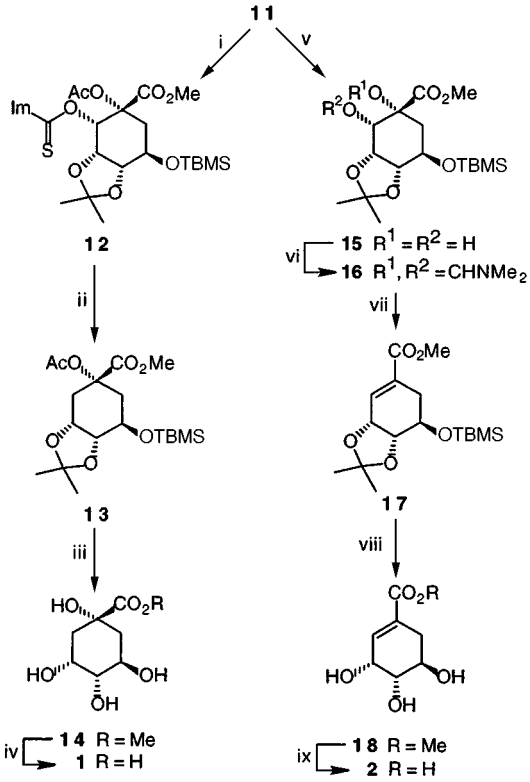
After acetylation, the resulting tertiary acetate **7**, $[\alpha]_D^{30}$ −61.3 (*c* 1.17, $CHCl_3$), was subjected to thermolysis in Ph_2O (*ca.* 280 °C) to give the cyclohexenone **8**, $[\alpha]_D^{29}$ +83.5 (*c* 0.53, $CHCl_3$), by retro-Diels–Alder reaction.

Although the stereochemistry of the catalytic osmylation of (+)-**8** could not be predicted, the reaction gave a readily separable 15 : 1 mixture from which the *cis*-diol **9**, $[\alpha]_D^{28}$ +82.8 (*c* 1.22, $CHCl_3$), having *syn* configuration to the acetoxy group, was obtained in 86% yield as the major product. The observed high diastereoselectivity may be due to the axially disposed acetoxy group in the molecule, which directs the stereochemistry of the dihydroxylation by interaction with OsO_4 forming a complex such as **8a**. After protection of the *cis*-diol functionality of **9** *via* reaction with $(MeO)_2CMe_2$ in the presence of PPTS,[12] the resulting acetonide **10** was reduced with $NaBH_4$ in MeOH at low temperature to give diastereoselectively the single alcohol **11**, $[\alpha]_D^{30}$ −15.5 (*c* 1.23, $CHCl_3$), which served as the common intermediate for (−)-quinic acid **1** and (−)-shikimic acid **2**. The overall yield of **11** from (−)-**3** was 57% (Scheme 2).

To obtain (−)-quinic acid **1**, **11** was first transformed into the imidazo-1-ylthiocarbonate[13] **12**, which then was treated with Bu_3SnH[13] to give the deoxygenated product **13**, $[\alpha]_D^{30}$ −23.2 (*c* 1.39, $CHCl_3$). Removal of the three oxygen protecting groups



Scheme 2 *Reagents and conditions*: i, NaH, $OC(OMe)_2$, THF, room temp., 23 h (86%); ii, O_2, KF, $P(OEt)_3$, DMSO, room temp., 22 h (90%); iii, Ac_2O, pyridine, room temp., 38 h (100%); iv, Ph_2O, reflux, 1 h (100%); v, OsO_4 (cat.), NMO, THF–H_2O (2 : 1), 0 °C, 72 h (86% 15 : 1 de); vi, $Me_2C(OMe)_2$, PPTS (cat.), 65 h; vii, $NaBH_4$, MeOH, −78 °C, 1.5 h (85% from **9**)



Scheme 3 *Reagens and conditions*: i, thiocarbonyl-1,1′-diimidazole, 50 °C, 14 h (100%); ii, Bu_3SnH, toluene, reflux, 9 h (80%); iii, CBr_4, MeOH, reflux, 19 h (86%); iv, NaOH, H_2O, roo temp., 13 h (100%); v, DBU, MeOH, −20 °C, 20 h; vi, $(MeO)_2CHNMe_2$, room temp., 23 h; vii, Tf_2O, Pr^i_2NEt, toluene, 50 °C, 1 h (80% from **11**); viii, 2% HCl–MeOH, room temp., 40 h (95%); ix, NaOH, THF–H_2O (1 : 1), room temp., 1 h (96%)

was carried out in one step by refluxing **13** with CBr_4 in MeOH[14] to give methyl quinate **14**, $[\alpha]_D^{30}$ −31.6 (*c* 1.45, MeOH), which was identical with authentic material derived from natural (−)-quinic acid **1**. Finally, **14** was hydrolyzed with NaOH to give (−)-quinic acid **1**, mp 167–168 °C, $[\alpha]_D^{30}$ −43.6 (*c* 2.03, H_2O) {lit.,[15] 162–163 °C, −42 to −44 (H_2O)}.

On the other hand, to obtain (−)-shikimic acid **2**, **11** was first deacetylated to give the *cis*-1,2-diol **15**, which afforded the cyclohexene **17**, $[\alpha]_D^{29}$ −19.7 (*c* 1.12, $CHCl_3$), *via* the cyclic amino acetal **16** on treatment with *N*,*N*-dimethylformamide dimethyl acetal followed by Tf_2O.[16] Exposure of **17** with dilute HCl in MeOH allowed spontaneous desilylation and removal of the acetonide group to give methyl shikimate **18**, $[\alpha]_D^{29}$ −130.0 (*c* 0.91, EtOH), which was identical with authentic material.[4] Finally, **18** was hydrolyzed with NaOH to give (−)-shikimic acid **2**, mp 184–185 °C, $[\alpha]_D^{25}$ −164.0 (*c* 0.59, H_2O) {lit.,[4] 184–186 °C, −163.7 (*c* 0.59, H_2O); lit.,[17] 184–186 °C, −170 (*c* 0.86, H_2O)} (Scheme 3).

We thank the Takeda Science Foundation for financial support.

Notes and References

† E-mail: konol@mail.cc.tohoku.ac.jp

‡ All new compounds had spectroscopic (IR, ^1H NMR, ^{13}C NMR, Mass) and analytical (combustion and/or high resolution mass) data consistent with the assigned structure.

1 For example: E. Haslam, *Progress in the Chemistry of Organic Natural Products*, ed. W. Herz, G. W. Kirby, R. E. Moore, W. Steglich and C. Tamm, Springer-Verlag, Wien, New York, 1996, vol. 69, p. 158; P. M. Dewick, *Nat. Prod. Rep.*, 1998, **15**, 17 and previous reports.
2 For example, M. C. Kozlowski, N. J. Tom, C. T. Seto, A. M. Sefler and P. A. Bartlett, *J. Am. Chem. Soc.*, 1995, **117**, 2128; C. U. Kim, W. Lew, M. A. Williams, H. Liu, L. Zhang, S. Swaminathan, N. Bischofberger, M. S. Chen, D. B. Mendl, C. Y. Tai, W. G. Laver and R. C. Stevens, *J. Am. Chem. Soc.*, 1997, **119**, 681.
3 Pertinent reviews for the synthesis of shikimic acid, see: M. M. Campbell, M. Sainsbury and P. A. Seavle, *Synthesis*, 1993, 179; S. Jiang and G. Singh, *Tetrahedron*, 1998, **54**, 4697; Natural (−)-quinic acid has been used as a versatile chiral building block: A. Barco, S. Benetti, C. D. Risi, P. Marchetti, G. P. Pollini and V. Zanirato, *Tetrahedron: Asymmetry*, 1997, **8**, 3515.
4 An alternative enantiocontrolled synthesis developed by the present group: T. Kamikubo and K. Ogasawara, *Chem. Lett.*, 1996, 987.
5 R. Grewe, W. Lorenzen and L. Vining, *Chem. Ber.*, 1954, **87**, 793; E. E. Smissman and M. A. Oxman, *J. Am. Chem. Soc.*, 1963, **85**, 2184; J. Wolinsky, R. Novak and R. Vasileff, *J. Org. Chem.*, 1964, **29**, 3596.
6 Conversion from D-arabinose, H. J. Bestmann and H. A. Heid, *Angew. Chem., Int. Ed. Engl.*, 1971, **10**, 336; see also R.-M. Meier and C. Tamm, *Helv. Chim. Acta.*, 1991, **79**, 807; H. Suemune, K. Matsuno, M. Uchida and K. Sakai, *Tetrahedron: Asymmetry*, 1992, **3**, 297.
7 K. Hiroya, Y. Kurihara and K. Ogasawara, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2287.
8 S. Otsuka and K. Tani, *Synthesis*, 1991, 665.
9 K. Ogasawara, *Pure Appl. Chem.*, 1994, **66**, 2119.
10 G. Büchi, R. Kulsa, K. Ogasawara and R. Rosati, *J. Am. Chem. Soc.*, 1970, **92**, 999.
11 H. Irie, J. Katakawa, M. Tomita and Y. Mizuno, *Chem. Lett.*, 1981, 637.
12 M. Miyashita, A. Yoshikoshi and P. A. Grieco, *J. Org. Chem.*, 1977, **42**, 3772.
13 D. H. R. Barton, W. B. Motherwell and A. Stange, *Synthesis*, 1981, 743; J. R. Rasmussen, C. J. Slinger, R. J. Kordish and D. D. Newman-Evans, *J. Org. Chem.*, 1981, **46**, 4843.
14 A. S.-Y. Lee, H.-C. Yeh and J.-J. Shie, *Tetrahedron Lett.*, 1998, **39**, 5249.
15 *Merck Index*, 1996, **12**, 8243.
16 J. L. King, B. A. Posner, K.-T. Mak and N. C. Yang, *Tetrahedron Lett.*, 1987, **34**, 3919.
17 G. W. Fleet, T. K. M. Shing and S. M. Warr, *J. Chem. Soc., Perkin Trans. 1*, 1984, 905.

Received in Cambridge, UK, 23rd July 1998; 8/05775C