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Efficient synthesis of (–)-methyl 3-*epi*-shikimate and methyl 3-*epi*-quinate by one-pot selective protection of *trans*-1,2-diols

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Abstract

trans-1,2-Diol protections of shikimic and quinic acids have been achieved by in situ formation of the protecting group (2,2,3,3-tetramethoxybutane). The synthetic utility of the protected derivatives is demonstrated by the preparation of (–)-methyl 3-*epi*-shikimate and methyl 3-*epi*-quinate through a new and efficient route from the parent acids. © 2000 Published by Elsevier Science Ltd.

Keywords: one-pot *trans*-1,2-diol protection; shikimic acid; quinic acid; 3-*epi*-shikimate; 3-*epi*-quinate.

1. Introduction

The shikimic acid biosynthetic pathway is utilized by plants, fungi and microorganisms for the synthesis of the aromatic L-α-amino acids phenylalanine, tyrosine and tryptophan, as well as the folate coenzymes and various isoprenoid quinones.[1] This metabolite, together with quinic acid, a substance intimately involved in the shikimic acid route, have received a great deal of attention as useful chiral building blocks and as optically active synthetic precursors for natural compounds.[2] Analogues of shikimate pathway intermediates that inhibit the action of the enzymes have been highlighted as materials with potential herbicidal, anti-fungal and antibiotic activity.[2c,3] C-3 shikimate and quinate derivatives are important tools in this area, since reactions at the C-3 hydroxyl group such as oxidation–reduction, phosphorylation or elimination, play an important role in the biosynthetic pathway.

In the last few years much attention has been focused on to the preparation of various C-3 substituted shikimate derivatives. Thus, synthesis of analogues of (–)-shikimic acid containing 3-amino,[4] 3-fluoro,[5] 3-chloro,[5b] 3-epi[4a,5b] and 3-phosphate[6] functionalities have been reported in the literature. Some of the published syntheses show limitations due to the difficulty of

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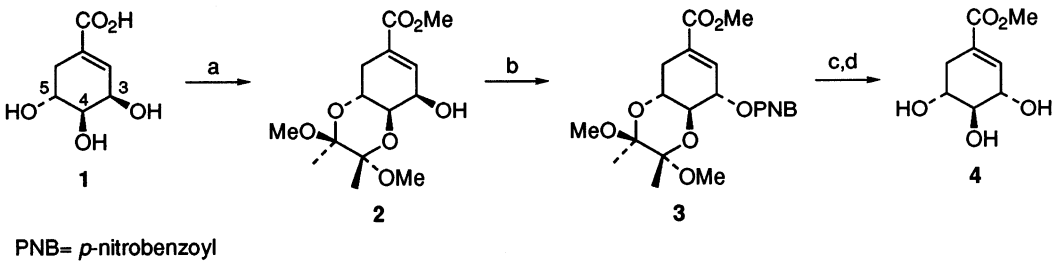
discerning between the three hydroxyl groups in the shikimic acid. In this paper we wish to report the selective protection of the 1,2-*trans* vicinal diol[7] in shikimic acid and quinic acid, in one-pot from commercially available starting materials, and avoiding the preparation of the protecting group.[8] The protection of the hydroxyl groups at the C-4 and C-5 positions allows a direct reaction at C-3, skipping the tedious task of several protection and deprotection steps. Taking advantage of this, we have synthesized (–)-methyl 3-*epi*-shikimate and methyl 3-*epi*-quinate by an efficient route from the parent acids.

2. Results and discussion

Reaction of shikimic acid **1** with 2.04 equivalents of butane-2,3-dione in methanol at 85°C in a sealed tube with a catalytic amount of (±)-CSA and 4.89 equivalents of trimethylorthoformate for 9 h, yields the 1,2-diacetal methyl ester **2** directly from the parent α-diketone (Scheme 1), in 80% isolated yield after flash chromatography. Protection of the *cis*-diol unit occurred only to a minor extent as shown by ^{1}H NMR analysis of the crude reaction mixture, in contrast with a 77:23 ratio (*trans*:*cis*-protection) when the reaction was carried out at 65°C. In compound **2**, the junction between the cyclohexene and the cyclic diacetal is *trans*-diequatorial, as shown by the coupling constant values of 11 Hz between H-4 and H-5, corresponding to an axial–axial disposition of both hydrogens (Fig. 1a). Likewise, H-3 has two coupling constants of 4.7 Hz, which are consistent with the pseudo-equatorial disposition of this hydrogen. Additionally,



Scheme 1. **a**: $(MeCO)_2$, $CH(OMe)_3$, (±)-CSA, MeOH, 85°C, sealed tube (80%). **b**: PNBOH, PPh_3, DEAD, THF (quantitative). **c**: MeONa, MeOH. **d**: CF_3CO_2H–H_2O (95%, two steps)

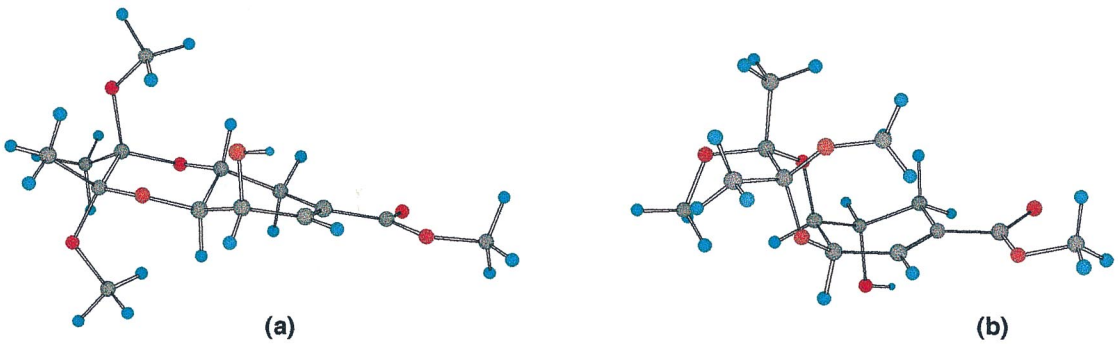
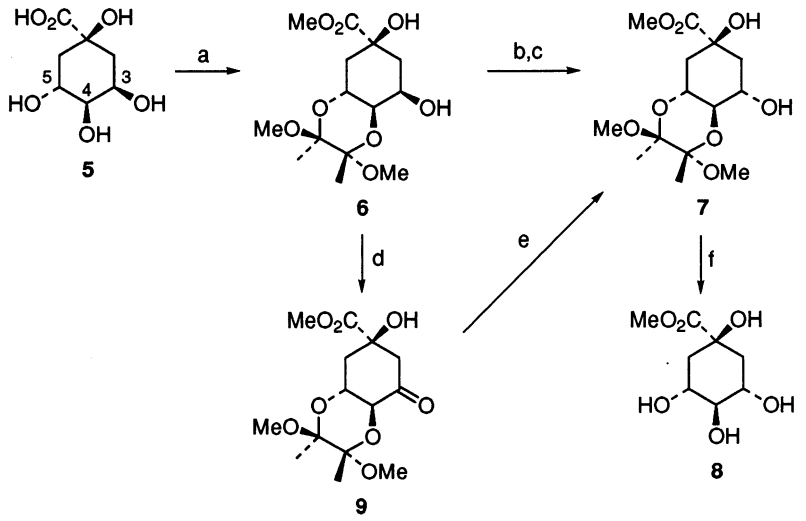


Figure 1. Conformations of methyl shikimate diacetals from NOESY experiments: (a) *trans*-1,2-protection; (b) *cis*-1,2-protection

NOESY experiments have shown the NOE effects of H-4 and H-5 with the methoxy groups, which are oriented in the axial position to obtain the maximum anomeric stabilization, whilst the methyl substituents are placed in the favored equatorial position. Similar studies on the minor *cis*-1,2-protected compound are in agreement with a chair conformation with H-4 and H-5 in an equatorial orientation and H-3 in a pseudo-axial one (Fig. 1b).

To invert the configuration at the C-3 position, Mitsunobu conditions were used. The reaction takes place in 2 h with total inversion of the configuration, giving quantitatively compound **3**. Deprotection of the *p*-nitrobenzoate ester with MeONa, and the subsequent removal of the diacetal moiety with a 19:1 trifluoroacetic acid:water mixture, easily converted **3** in 95% yield into the corresponding (–)-methyl 3-*epi*-shikimate. Its spectral data are consistent with the reported values.[5b]

To the best of our knowledge, no report exists for the chemical synthesis of methyl 3-*epi*-quinate **8**. Thus, the above efficient methodology was applied to quinic acid **5** (Scheme 2). In this case, compound **6** was formed as an unique and enantiopure product in the *one-pot* selective protection of the *trans*-1,2-diol. The reaction takes place under reflux in 1 h with 90% yield after recrystallization. Previous molecular mechanics calculations[9] in quinic and shikimic acids revealed a small energy difference between both possible conformations in shikimic acid and a large one for quinic acid, which is in agreement with the absence of *cis*-1,2-protected derivative in quinic acid and the presence as minor compound in shikimic acid.



Scheme 2. **a**: $(MeCO)_2$, $CH(OMe)_3$, (±)-CSA, MeOH, reflux (90%). **b**: PNBOH, PPh_3, DIAD, toluene. **c**: MeONa, MeOH (50%, two steps). **d**: PCC, CH_2Cl_2 (82%). **e**: $NaBH(OAc)_3$, CH_2Cl_2, 0°C→rt (80%). **f**: CF_3CO_2H–H_2O (quantitative)

A Mitsunobu reaction on the free secondary alcohol in compound **6** led to the C-3 *p*-nitrobenzoate ester together with the corresponding elimination product in a 4.5:1 ratio, respectively. As a consequence, derivative **7** was obtained with a moderate yield of 50%. An alternative inversion, using CsF and benzoic acid in DMF on the tosylate derivative, did not improve the previous results. The inversion was best carried out by oxidation of diol **6** with PCC, and the subsequent selective reduction of ketone **9** with sodium triacetoxyborohydride. This afforded almost exclusively diol **7** (diastereomers **7** and **6** were obtained in a 24:1 ratio,

respectively, and **7** was isolated by flash chromatography using CH_2Cl_2:Et_2O 1:1 as eluent). Removal of the protecting group with aqueous trifluoroacetic acid provided methyl 3-*epi*-quinate **8**.[10]

In conclusion, we have introduced the use of 1,2-diacetals in a one-pot procedure for the regioselective protection of the 4,5-hydroxyl groups of shikimic and quinic acids from commercially available reagents. Thus, esterification of shikimic or quinic acids, preparation of the protecting group, and diacetal formation were achieved simultaneously. This direct and selective *trans* 1,2-vicinal diol protection allowed us to synthesize (−)-methyl 3-*epi*-shikimate and methyl 3-*epi*-quinate by short and efficient routes.

Acknowledgements

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10. Compound **8**: white hygroscopic solid; ^{1}H NMR (MeOH-d_4, 200.13 MHz): δ 1.95 (dd, 2H, H_{2a}+H_{6a}, $^2J_{HH}$ 12.7, $^3J_{HH}$ 11.6 Hz), 2.21 (m, 2H, H_{2e}+H_{6e}), 3.36 (dd, 1H, H_4, $^3J_{HH}\sim$9 Hz), 3.91 (m, 2H, H_3+H_5), and 3.93 (s, 3H, O*Me*); ^{13}C NMR (MeOD-d_4, 75.5 MHz): δ 41.9 (C_2+C_6), 53.3 (O*Me*), 70.8 (C_3+C_5), 75 (C_1), 81.7 (C_4), and 177 (C=O); IR (NaCl): ν 3351, 2934, and 1730 cm^{-1}; ESI Positive: 229.1 (M+Na)$^+$.