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Asymmetric Routes to the Trisporic Acids via Chiral Bicyclic Lactams

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Department of Chemistry, Colorado State University, Fort Collins, CO 80523-1872, U. S. A. Received 8 January 1999; accepted 22 February 1999 Summary: Two synthetic approaches to the title compounds using the chiral non-racemic lactam 3 via additions to the lactam carbonyl lead to the requisite chiral cyclohexen-2-ones. © 1999 Elsevier Science Ltd. All rights reserved.

Naturally occurring fungal hormones known as the trisporic acids¹ (series A, B, C) are a class of C_{18} isoprenoids isolated from the mated cultures of *Mucor mucedo* and *Blakeska trispora*. Extensive studies on these systems have indicated that they originate from β -carotene and have been shown to be necessary for the sexual reproduction of the fungi.²

Successful synthetic efforts to reach these interesting systems have been reported ³⁻⁸ and the absolute configurations at C-1 and C-13 have been established.^{3,9} In an attempt to develop a general enantioselective route to these systems, we have employed chiral lactams 1 which have already been shown to produce 4, 4-dialkyl-2-cyclohexenones 2 ($R_1 = H$) in high enantiomeric purity and good yields.¹⁰

Trisporic Acids and Alcohols



Our plan involved the use of the readily prepared hydroxy lactam 3^{10} which was transformed into its *tert*-butyldimethylsilyl ether (TBS) 4 and then acylated (*n*-BuLi, (Boc)₂O) to give 5 as 1:1 mixture of diastereomers. Removal of the TBS group (TBAF, THF, rt) furnished the hydroxy ester 6 (58%; 2 steps). The hydroxy ester was deprotonated (2.0 eq *s*-BuLi, THF, -78 °C) and C-alkylated with MeI, to give the quaternary substituted lactam 7 in 87% yield as a single diastereomer (NMR, HPLC). The latter was O-methylated to 8 (NaH, MeI) followed by reduction (LiBH₄, Et₂O-MeOH, 0 °C) to the primary alcohol 9 (mp 88-90 °C, 85% yield). This sequence was carried out in 7 synthetic steps in 31% overall yield from 3. Furthermore, the absolute configuration of 9 was verified by a single crystal X-ray determination.



We believed that a vinyllithium reagent added directly to the lactam carbonyl of 9 followed by hydrolysis would lead directly to the properly substituted cyclohexenone 11. To this effect, β -lithiostyrene (β -bromostyrene, Et₂O, *t*-BuLi, -78 °C) was treated with lactam 9 (-78 °C to 0 °C, 1 h) and the resulting carbinol 10 was immediately subjected to hydrolysis (Bu₄NH₂PO₄, EtOH, H₂O, reflux, 1 h) to provide cyclohexenone 11¹¹ in 16-20% over 3 steps from 9. This model experiment encouraged us to utilize the fully substituted side chain 12c, prepared from 12a and 12b following literature methods (Scheme 3).¹² Vinyl bromide 12c was metallated with *t*-BuLi (-78 °C, Et₂O) and 5.0 equiv. of the lithio derivative were added to the lactam 9. The crude carbinolamine 13 was directly hydrolyzed as above to produce the cyclohexenone ketal 14, presumably via the diketone and subsequent, spontaneous aldol cyclization. The low yield (8-10%; 3 steps) obtained for 14 may be due to the poor aldol step which has previously been experienced by Trost⁴ and Edwards⁷ (10-20% yield). The excessive functionality of the diketone could also have been a major factor for this disappointing yield. Even simpler diketones reported by Isoe¹³ gave only moderate yields of cyclohexenone.⁸ Furthermore, our cyclization of 10 \rightarrow 11 also proceeded in a moderate 16% overall yield. The production of 14, if made more efficient, would constitute the most direct route to the trisporic acids and related derivatives.





Due to the difficulties in reaching 14 directly, we examined another route to trisporic acids using chiral lactams 15-18, prepared as shown in Scheme 4. Rather than introduce the fully constructed side chain 12c, we opted to simply reduce the lactam 18 to 19 using Red-Al[®]. If hydrolysis of the latter could be stopped at the keto-aldehyde stage, 20, this would allow the introduction of a simpler lithio-acetylene to afford 21. This



indeed did occur under ambient temperature to produce keto aldehyde 20 in 40-50% yield ($Bu_4NH_2PO_4$, EtOH, H_2O , rt, 24 h). Addition of lithio TMS-acetylide, with CeCl₃ to avoid enolization, gave 21 as a mixture of alcohols, which were directly oxidized to the diketone and cyclized to 22 (Scheme 3). The yield for the latter two steps was 68%. The acquisition of (R)-(+)-22 and application of Suzuki's method¹⁴, which previously gave racemic benzyl ether 24, should access the trisporol system albeit as its methyl ether 23. The synthesis, as described herein, would lead to the unnatural 1R configuration 25. However, reversing the order of addition to 3 would lead to the natural system. This approach to the acetylenic cyclohexenone 22, in

enantiomerically pure form, now allows many of the trisporic acid and alcohols to be accessed without the need to endure poor yields in the late stage aldol cyclization.

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- 11. Satisfactory physical data have been obtained for all compounds. Data for 11: $[\alpha]_D + 20.6^{\circ}$ (c 0.5, CHCl₃); UV (EtOH) 302, 247 nm; IR 3426, 1651 cm⁻¹; ¹H-NMR, ¹³C-NMR, HRMS (MH⁺) *m/z* 257.1545). **22** $[\alpha]_D$ 33.1 (c 0.3, CHCl₃); UV (EtOH) 300, 240 nm; IR 2084, 1668 cm⁻¹; ¹H-NMR, ¹³C-NMR, HRMS (FAB); Calc'd for C₁₂H₁₆O₂ (M⁺) 192.1229, found (MH⁺) 193.1235.
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