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Asymmetric Routes to the Trisporic Acids via Chiral Bicyclic Lactams

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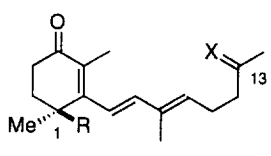
Summary: *Two synthetic approaches to the title compounds using the chiral non-racemic lactam 3 via additions to the lactam carbonyl lead to the requisite chiral cyclohexen-2-ones.*

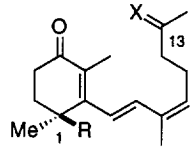
Naturally occurring fungal hormones known as the trisporic acids[1] (series A, B, C) are a class of C_{18} isoprenoids isolated from the mated cultures of *Mucor mucedo* and *Blakeska trispora.* Extensive studies on these systems have indicated that they originate from β-carotene and have been shown 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]

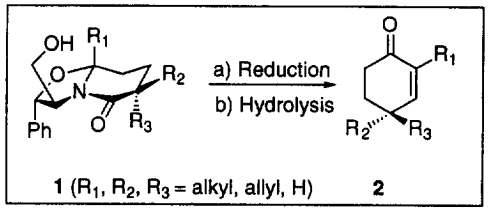
Trisporic Acids and Alcohols



Series A



Series B, C



1 (R_1, R_2, R_3 = alkyl, allyl, H) **2**

R = CO_2H, CO_2Me, CH_2OH
X = O, OH, H

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 ($LiBH_4$, Et_2O-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.

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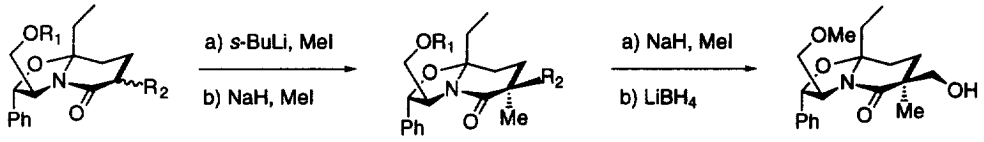
Scheme 1



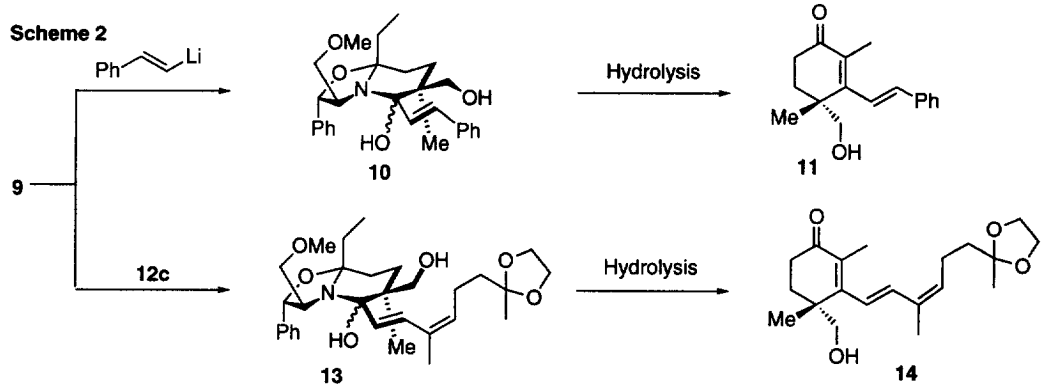
3, $R_1 = R_2 = H$
4, R_1 = TBS, $R_2 = H$
5, R_1 = TBS, $R_2 = CO_2Bu^t$
6, $R_1 = H$, $R_2 = CO_2Bu^t$

7, $R_2 = CO_2Bu^t$, $R_1 = H$
8, $R_2 = CO_2Bu^t$, R_1 = Me

9

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, Et_2O, *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 ($Bu_4NH_2PO_4$, EtOH, H_2O, reflux, 1 h) to provide cyclohexenone **11**[11] 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, Et_2O) 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 Trost[4] and Edwards[7] (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 Isoe[13] gave only moderate yields of cyclohexenone.[8] Furthermore, our cyclization of **10** → **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.

Scheme 2



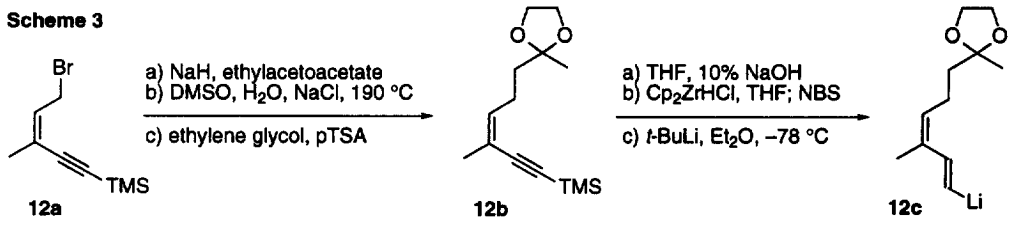
10

11

13

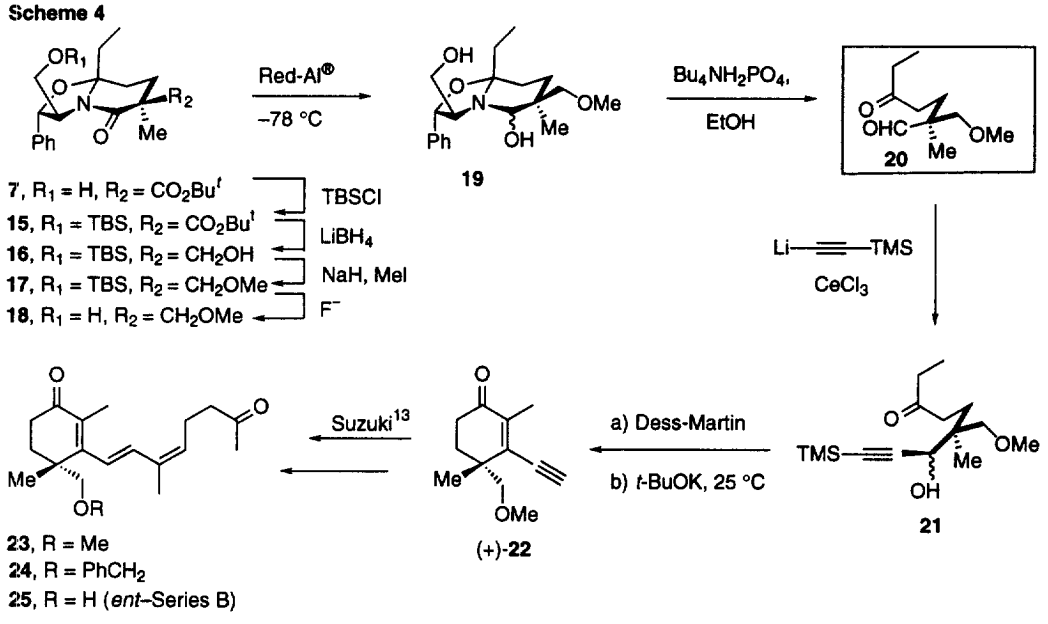
14

Scheme 3



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

Scheme 4



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 $CeCl_3$ 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 method[14], 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.

Acknowledgements.

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11. Satisfactory physical data have been obtained for all compounds. Data for **11**: $[\alpha]_D$ + 20.6 ° (c 0.5, $CHCl_3$); UV (EtOH) 302, 247 nm; IR 3426, 1651 cm^{-1}; ^{1}H-NMR, ^{13}C-NMR, HRMS (MH^+) *m/z* 257.1545). **22** $[\alpha]_D$ 33.1 (c 0.3, $CHCl_3$); UV (EtOH) 300, 240 nm; IR 2084, 1668 cm^{-1}; ^{1}H-NMR, ^{13}C-NMR, HRMS (FAB); Calc'd for $C_{12}H_{16}O_2$ (M^+) 192.1229, found (MH^+) 193.1235.

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