Total Synthesis of Muconin by Efficient Assembly of Chiral Building Blocks

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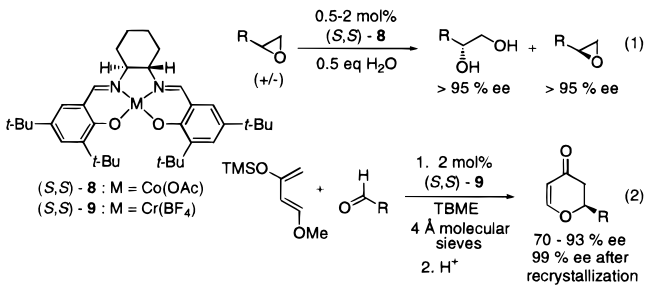
Received June 8, 1998

Muconin (**1**) is a novel tetrahydropyran-bearing acetogenin isolated from *Rollinia mucosa* that has exhibited potent and selective in vitro cytotoxicities against pancreatic and breast tumor cell lines.[1] We considered the possibility of preparing **1** by the convergent assembly of readily accessible chiral units (Scheme 1). We describe herein the total synthesis of muconin—the first of any THP-bearing Annonaceous acetogenin[2]—by taking advantage of such a chiral building block approach.

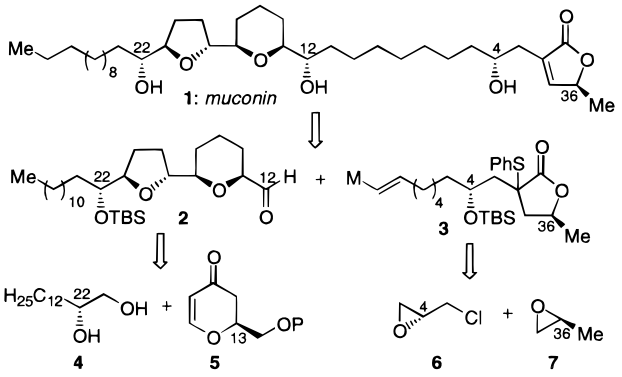
Our laboratories uncovered recently a highly effective



method for the hydrolytic kinetic resolution (HKR) of terminal epoxides catalyzed by cobalt complex **8** (eq 1).[3] The HKR provides practical access to both terminal epoxides and 1,2-diols in highly enantioenriched form. The commercial availability on a bulk scale of racemic terminal epoxides such as tetradecene oxide, epichlorohydrin, and propylene oxide render these attractive starting materials for the synthesis of muconin. The fourth requisite building block, dihydropyran **5**, is also readily accessed in enantioenriched form using the recently discovered hetero-Diels−Alder condensation of 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene with aldehydes catalyzed by chromium complex **9** (eq 2).[4]

To synthesize fragment **2**, the HKR of (±)-tetradecene oxide using 0.5 mol % of complex (*S*,*S*)-**8** in TBME and 0.5 equiv of H_2O afforded (*R*)-tetradecane-1,2-diol **4** in >99% ee and in 90% of the theoretical yield.[5] Selective protection of the secondary hydroxyl group was effected by the method of Yamamoto using trimethyl orthoformate and DIBALH.[6] The resulting primary alcohol **10** was transformed to the corresponding aldehyde without detectable epimerization by means of TEMPO-catalyzed oxidation with hypochlorite.[7] Chelation-controlled addition of vinylmagnesium bromide in

Scheme 1



CH_2Cl_2 with $MgBr_2{\cdot}OEt_2$[8] at −78 °C provided the desired allylic alcohol in 74% yield and >100:1 diastereoselectivity. This material was converted to acid **11** in 92% yield by alkylation with sodium iodoacetate in THF.

Pyranol **12** was constructed by the hetero-Diels−Alder condensation of 1-methoxy-3-[(trimethylsilyl)oxy]-1,3-butadiene with *p*-bromobenzyloxyacetaldehyde catalyzed by 2 mol % (*S*,*S*)-**9** followed by diastereoselective Luche reduction.[9] The moderate enantioselectivity of the catalytic reaction (80% ee) was reconciled by recrystallization of the dihydropyranone condensation product to 99% ee and in good yield. Esterification of **12** with acid **11** was effected cleanly under EDC coupling conditions. The corresponding silyl ketene acetal was generated with LDA in 4:1 THF/HMPA and in situ trapping with TMSCl.[10] Ireland−Claisen rearrangement[11] occurred upon elevation of the reaction temperature to 50 °C, with formation of the 2,6-cis-disubstituted dihydropyran isolated as the methyl ester in 81% yield and 5:1 diastereoselectivity at C(18). The observed preferential formation of the threo stereoisomer is attributable to sigmatropic rearrangement of the *Z*-silyl ketene acetal through a boatlike transition state.[12] The methyl ester was converted to the terminal olefin **13** in 70% yield by means of a one-pot DIBALH reduction/Wittig olefination sequence.[13] The MOM protecting group proved labile in subsequent steps of the synthesis and was therefore exchanged for a TBS group at this stage. Ring-closing metathesis[14] yielded the desired dihydrofuran in excellent yield. This material was reduced to the THF−THP derivative with concomitant removal of the PBB protecting group by hydrogenation using 10% Pd/C. The resulting primary alcohol was oxidized with Dess−Martin periodinane[15] to yield aldehyde **2**, which was used without purification.

To synthesize fragment **3**, (*R*)-epichlorohydrin **6** was readily obtained in >99% ee and 82% of theoretical yield by HKR of racemic epoxide using 0.5 mol % of (*S*,*S*)-**8** and 0.55 equiv of water. Copper(I)-catalyzed[16] epoxide ring-opening

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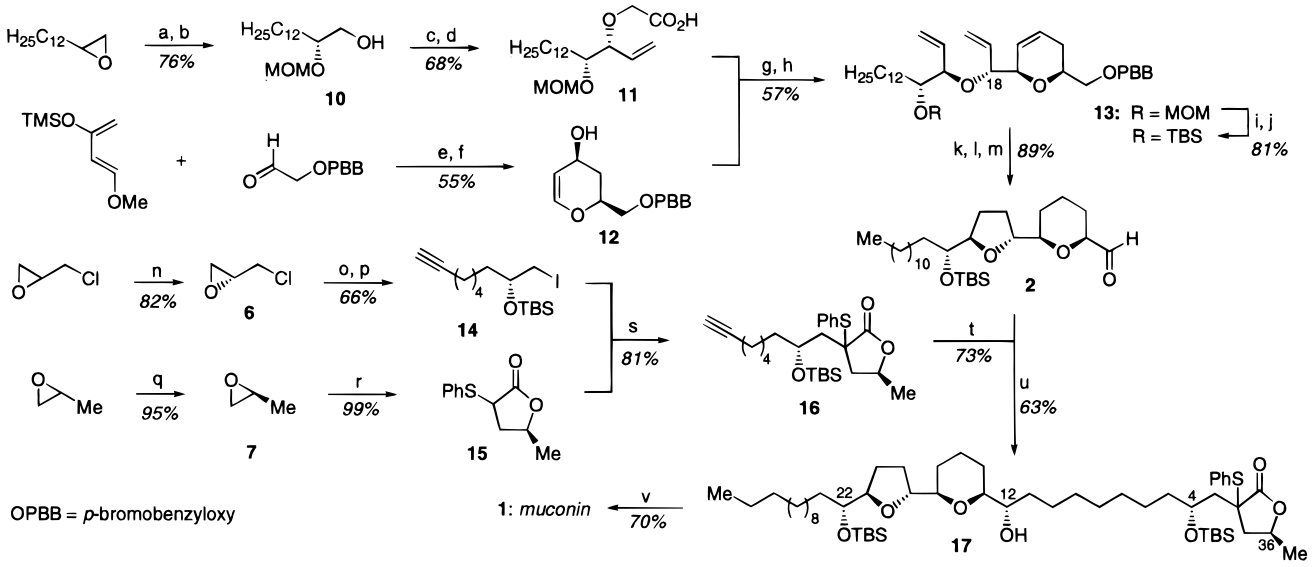
S0022-3263(98)01076-7 CCC: $15.00
Published on Web 07/08/1998

Scheme 2[a]



[a] Reagents: (a) 0.5 mol % (*S*,*S*)-**8**, 0.5 equiv of H_2O, TBME, 0 °C → rt, 90%, 99% ee; (b) (i) $CH(OMe)_3$, cat. CSA, CH_2Cl_2, rt; (ii) DIBALH, CH_2Cl_2, −78 °C, 84%; (c) (i) cat. TEMPO, NaBr, $NaHCO_3$, NaOCl, PhMe/EtOAc 1:1, H_2O, 0 °C; (ii) $MgBr_2{\cdot}OEt_2$, $CH_2{=}CHMgBr$, CH_2Cl_2, −78 °C, 74%; (d) (i) NaH, THF, 0 °C; (ii) ICH_2CO_2Na, 0 °C → rt, 92%; (e) (i) 2 mol % (*S*,*S*)-**9**, TBME, 4 Å molecular sieves, −30 °C; (ii) TFA, rt; (iii) recrystallization, 72% yield, 99% ee; (f) $CeCl_3{\cdot}H_2O$, MeOH, $NaBH_4$, EtOH, −78 → 0 °C, 76%; (g) (i) EDC, cat. DMAP, CH_2Cl_2, 0 °C; (ii) LDA, TMSCl, THF/HMPA 4:1, −78 → +50 °C; (iii) CH_2N_2, 82%; (h) (i) DIBALH, PhMe, −78 °C; (ii) $CH_2{=}PPh_3$, THF, −78 → +40 °C, 70%; (i) TMSBr, 4 Å molecular sieves, CH_2Cl_2, −30 °C, 82%; (j) TBSOTf, 2,6-lutidine, 0 °C, 99%; (k) 5 mol % $Mo(CHMe_2Ph)(NAr)(OCMe(CF_3)_2)_2$, PhH, rt, 99%; (l) 10% Pd/C, $NaHCO_3$, EtOH, H_2 (5 atm), rt, 95%; (m) Dess−Martin periodinane, pyridine, CH_2Cl_2, rt, 95% (crude yield); (n) 0.5 mol % (*S*,*S*)-**8**, 0.55 equiv of H_2O, 0 °C → rt, 82%, 99% ee; (o) 1-(trimethylsilyl)-6-bromo-1-hexyne, Mg, CuI, THF, −78 °C, 88%; (p) (i) NaOH, Et_2O, rt; (ii) TBAF, THF, rt; (iii) LiI, AcOH, THF, rt; (iv) TBSCl, imidazole, DMF, rt, 75%; (q) 0.2 mol % (*S*,*S*)-**8**, 0.55 equiv of H_2O, 0 °C → rt, 95%, 98% ee; (r) (i) LDA, THF, phenylthioacetic acid, rt; (ii) *p*TsOH, benzene, rt, 99%; (s) LDA, THF, HMPA, rt, 81%; (t) (i) $(cyclohexyl)_2BH$, hexane, rt; (ii) $ZnEt_2$, hexane, **2**, −78 → −15 °C, 73%; (u) (i) Swern; (ii) $Zn(BH_4)_2$, Et_2O, cyclohexene, CH_2Cl_2, −78 → 0 °C; (iii) 10 mol % PtO_2, THF, H_2 (1 atm), 63%; (v) (i) *m*-CPBA, CH_2Cl_2, 0 °C; (ii) PhMe, Δ; (iii) 5% AcCl in MeOH, rt, 70%.

using the Grignard reagent derived from 1-(trimethylsilyl)-6-bromo-1-hexyne[17] gave the corresponding chlorohydrin in 88% yield, and this product was converted to the TBS-protected iodohydrin **14** in 75% yield. Lactone **15**[18] was readily prepared in quantitative yield from phenylthioacetic acid and (*S*)-propylene oxide, the latter obtained by a highly efficient HKR with catalyst (*R*,*R*)-**8**. Alkylation of the enolate derived from **15** with iodohydrin **14** afforded **16** in 81% yield.[19] Elimination of the phenyl sulfide was deferred to the end of the synthesis in order to avoid possible epimerization of the base-sensitive butenolide in the intervening steps.[20]

The key fragment coupling was accomplished by hydroboration of **16** and transmetalation, followed by addition of aldehyde **2** to the resulting vinylzinc derivative.[21] The addition product was obtained in 73% yield as a 3.6:1 mixture of diastereomers favoring the undesired C(12) epimer.[22] Exploration of a variety of reaction conditions failed to uncover any effective method for the chelation-controlled alkylation of **2**, presumably as a result of the ion-sequestering capabilities of the THF−THP unit in this substrate. The desired C(12)−(*S*) stereochemistry was installed by means of a Swern oxidation/$Zn(BH_4)_2$[23] reduction sequence to provide the desired diastereomer with 7:1 diastereoselectivity. Hydrogenation over PtO_2 afforded diastereomerically pure lactone **17** after isolation by flash chromatography in 63% overall yield for the three-step sequence. Oxidation of the phenyl sulfide with *m*-CPBA, followed by thermally induced elimination to the butenolide and a final deprotection step, provided muconin **1** with spectral properties identical to those of the natural product.

With the ongoing development of powerful new asymmetric catalytic reactions, the synthetic chemist's reliance on Nature's pool of optically active building blocks is diminishing. The synthesis of stereochemically complex targets by assembly of chiral components[24] becomes not only more tenable, but also highly attractive from a strategic standpoint since it is readily amenable to the preparation of stereochemical and structural analogues.

Acknowledgment. This work was sponsored by the NIH (GM-43214). We would like to thank Prof. J. L. McLaughlin for providing spectral data of muconin. We acknowledge predoctoral fellowship support to S.E.S. from the Ford Foundation and postdoctoral fellowship support to J.B. from the Knut and Alice Wallenberg Foundation.

Supporting Information Available: Complete experimental procedures, chiral chromatographic analyses of racemic and enantiomerically enriched **4**−**6**, and ^1H NMR spectra of key intermediates (47 pages).

JO9810765

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