AN ENANTIOCONTROLLED TOTAL SYNTHESIS OF (-)-XANTHORRHIZOL

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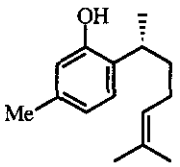
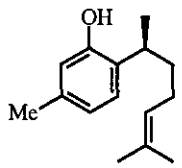
Abstract - An efficient and enantiocontrolled total synthesis of natural (-)-xanthorrhizol (**3**) has been accomplished by employing the lipase-mediated asymmetric acetylation of the σ-symmetrical prochiral 2-aryl-1,3-propanediol (**7**) leading to the formation of the optically enriched monoacetate (**6**) as the key step.

The aromatic bisabolene sesquiterpenoids[1] are members widely distributed in nature. Some of them possess interesting biological properties and are isolated from both terrestrial plants and marine sources in both enantiomeric forms;[2] e.g. (-)-curcuphenol (**1**), which exhibits antifungal and anticancer activities, is a plant constituent and its optical antipode (+)-curcuphenol (**2**) has been isolated from the Caribbean sponge. Accordingly, the development of an efficient and general synthetic route to both enantiomers of these sesquiterpenoids is of significant value. Xanthorrhizol (**3**)[3] was first isolated by Kochendoerfer *et al.* from rhizomes of *Curcuma xanthorrhiza* Roxb., which has been utilized as a tonic in Indonesia and as a choleretic drug in Europe. Afterward, it was also isolated from the same plant as an antitumor constituent by Itokawa *et al.*[4] As regards its pharmacological activities, it has been shown that xanthorrhizol interacts with cytochrome P-450 to inhibit the metabolism of pentobarbital.[5] At the outset of our investigations, three syntheses of the racemate[6] and the conversion of (+)-*ar*-turmerone to the natural antipode (+)-(**3**)[7] had been reported. Recently, the first asymmetric synthesis of (+)-(**3**) has been completed by Meyers.[8] We present here an efficient and enantioselective total synthesis of natural (-)-xanthorrhizol (**3**) based on the asymmetric construction methodology for the benzylic tertiary stereogenic center by employing chemoenzymatic transformation.[9] (Figure 1)

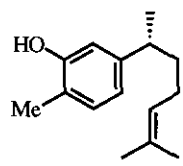
We envisaged that a pivotal construction of the benzylic tertiary stereogenic center in **3** can be realized by



(-)-curcuphenol **1**



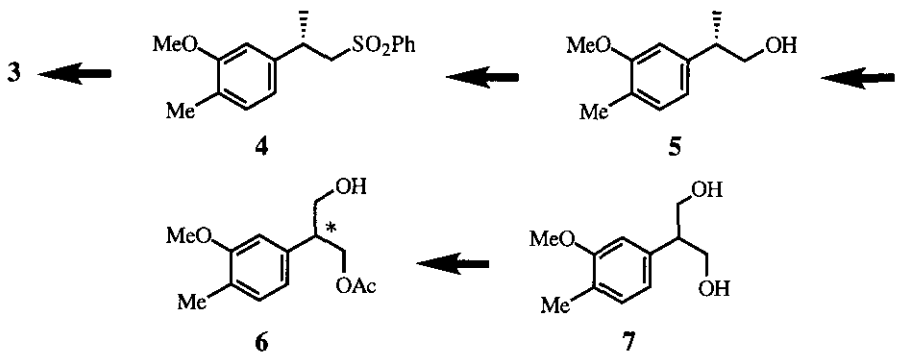
(+)-curcuphenol **2**



(-)-xanthorrhizol **3**

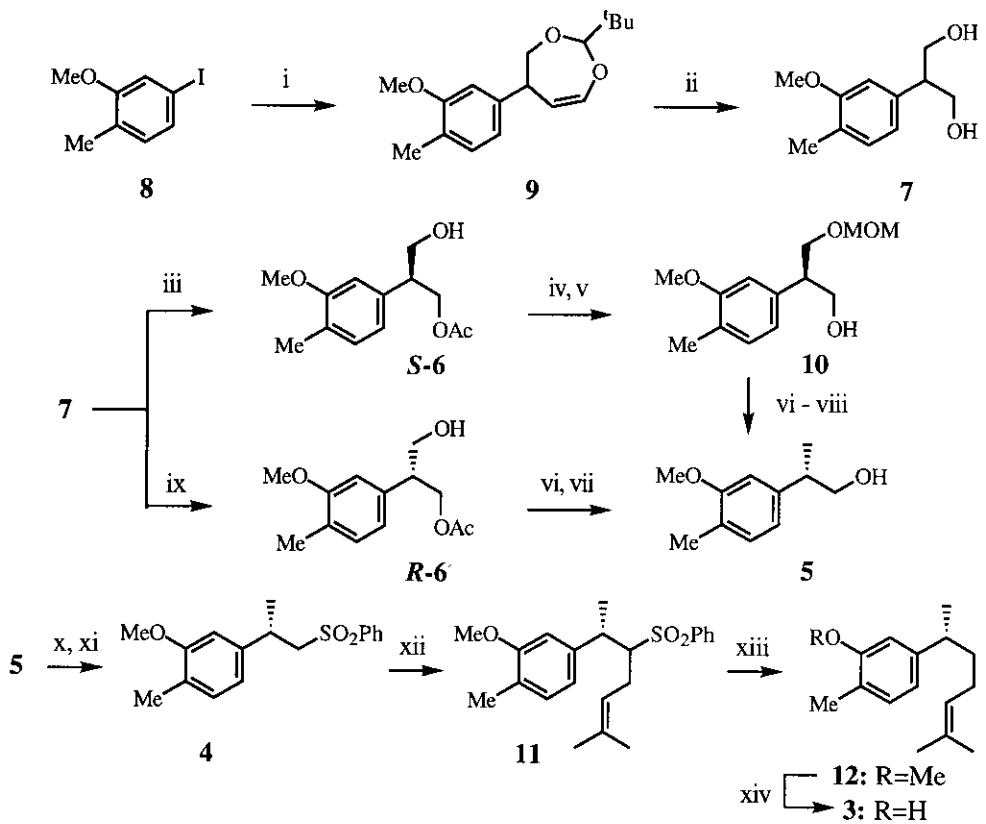
Figure 1

employing the lipase-catalyzed asymmetric acetylation of the σ-symmetrical prochiral 2-aryl-1,3-propanediol (**7**) to the optically enriched monoacetate (**6**). Transformation of **6** into the sulfone (**4**) via the alcohol (**5**) followed by sequential prenylation, reductive removal of the benzenesulfonyl group and demethylation would afford (-)-xanthorrhizol (**3**) as outlined in Scheme 1. In our plan, it should be mentioned that the monoacetate (**6**) would be utilized as a common intermediate for the production of both enantiomers of **3** by the chemoselective functional group discrimination of both the hydroxy and acetoxy moieties in **6**.



Scheme 1

Heck reaction[10] between 4-iodo-2-methoxytoluene (**8**), prepared from 4-bromo-2-methoxytoluene[11] according to the procedure of Suzuki,[12] and 2-*tert*-butyl-4,7-dihydro-1,3-dioxepine utilizing a catalytic amount of palladium acetate, triphenylphosphine (Ph_3P) and Hünig base ($^iPr_2NEt$) in DMF at 80 °C provided the coupled product (**9**), which was submitted to ozonolysis followed by reductive workup with sodium borohydride ($NaBH_4$) to give the prochiral diol (**7**) in 47% yield from **8**. With the substrate for the chemoenzymatic transformation in hand, we explored the optimum conditions of asymmetric acetylation utilizing some lipases. Of these, *Candida antarctica* lipase (CAL)-catalyzed acetylation conditions with vinyl acetate as an acyl donor in benzene produced cleanly the optically active monoacetate *S*-(**6**), $[\alpha]_D$ -16.7° (c=1.51, $CHCl_3$), in 19% yield.[13] The enantiomeric excess of *S*-**6** was determined to be 94% ee by HPLC analysis on a Chiralcel OD column. The absolute configuration of the benzylic stereogenic center was



Scheme 2. ***Reagents & Conditions***: i, 2-*tert*-butyl-4,7-dihydro-1,3-dioxepine, $Pd(OAc)_2$, Ph_3P, $^iPr_2NEt$, DMF, 80°C, 75%; ii, O_3, CH_2Cl_2:MeOH (1:1), -78°C then $NaBH_4$, rt, 63%; iii, CAL, vinyl acetate, Et_2O, rt, 19%; iv, MOMCl, $^iPr_2NEt$, 4-DMAP, CH_2Cl_2, rt, 81%; v, $LiAlH_4$, THF, rt; vi, TsCl, Et_3N, 4-DMAP, CH_2Cl_2, rt; vii, $NaBH_4$, DMSO, 60°C, 72% (3 steps) for the MOM ether **10**, 65% (2 steps) for ***R*-6**; viii, 10% HCl (aq.), MeOH, rt, 95%; ix, PPL, vinyl acetate, Et_2O, 39°C, 95%; x, $^nBu_3P$, Ph_2S_2, pyridine, rt, 84%; xi, MCPBA, $KHCO_3$, CH_2Cl_2, rt, 100%; xii, ^{n}BuLi, prenyl bromide, HMPA, THF, -78°C, 82%; xiii, 5% Na-Hg, Na_2HPO_4, MeOH, rt, 83%; xiv, L-Selectride®, THF, reflux, 78%.

deduced to be *S* in terms of the empirical rule[14] based on the chemical shift of the corresponding MTPA ester. The confirmation was made by the eventual conversion of *S*-**6** into *O*-methylxanthorrhizol (**12**).[7] For the synthesis of the natural enantiomer of **3**, however, the optical antipode of *S*-**6** was necessary. PPL-catalyzed acetylation of **7** in ether proved to be the best choice for the purpose and the desired monoacetate *R*-(**6**), $[\alpha]_D$ +14.3° (c=0.95, CHCl3), with 83% ee was obtained in 95% yield. The *R*-monoacetate thus obtained was then tosylated and reductively deoxygenated with NaBH4 in hot DMSO[15] to provide the *S*-alcohol (**5**) in 65% yield for the 2 steps. The monoacetate *S*-(**6**) with *S*-configuration, which was derived with higher enantioselectivity (94% ee) utilizing CAL, was successfully converted into

S-**5** *via* a five-step sequence of reactions. Thus, methoxymethylation of *S*-**6** followed by alkaline hydrolysis gave **10**, which was treated with the deoxygenation conditions adapted for *R*-**6** to provide, after acidic hydrolysis, the *S*-alcohol (**5**) in 55% overall yield. The enantioconvergent process could be established in this system. Hata reaction[16] of the alcohol (**5**) with diphenyl disulfide in the presence of $^{n}Bu_3P$ provided the corresponding sulfide, which was oxidized with *m*-chloroperbenzoic acid to give the sulfone (**4**) in 84% yield. Fortunately, **4** was crystallized and the enantiomerically pure sulfone was obtained by a single recrystallization from hexane. Installation of the prenyl moiety was realized by treatment of **4** with n-butyllithium followed by prenyl bromide to afford **11**. Reductive removal of the benzenesulfonyl group in **11** was achieved by treating with 5% sodium amalgam in buffered methanol to give *O*-methylxanthorrhizol (**12**), $[\alpha]_D$ -38.5° (c=0.42, $CHCl_3$) {lit.,[7] $[\alpha]_D$ +51.6°, for *S*-enantiomer}. Finally, on exposure of **12** to L-Selectride®,[17] the methyl ether in **12** was cleanly cleaved to produce (-)-xanthorrhizol (**3**), $[\alpha]_D$ -54° (c=0.13, $CHCl_3$) {lit.,[5] $[\alpha]_D$ -58° (c=1.0, $CHCl_3$)} in 78% yield, whose ^{1}H-NMR properties were identical with those of natural product (**3**).[6a] (Scheme 2)

In summary, we have demonstrated a methodology for the general construction of optically active aromatic bisabolene sesquiterpenoids in both enantiomeric forms, exemplified by an enantiocontrolled total synthesis of natural (-)-xanthorrhizol.

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