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

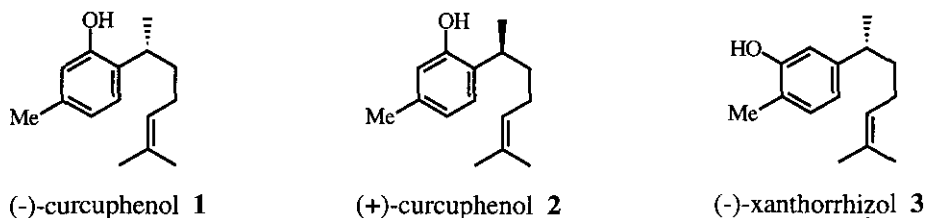(-)-curcuphenol **1**   (+)-curcuphenol **2**   (-)-xanthorrhizol **3**

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**.
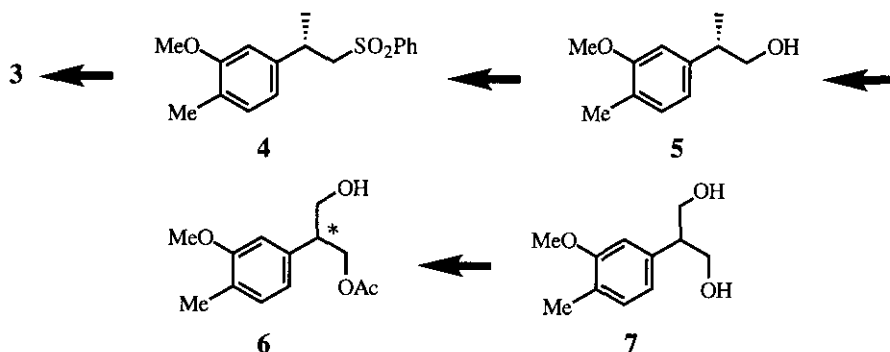
Scheme 1

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 (Ph3P) and Hünig base (^{i}Pr2NEt) in DMF at 80 °C

provided the coupled product (**9**), which was submitted to ozonolysis followed by reductive workup with

sodium borohydride (NaBH4) 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, CHCl3), 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
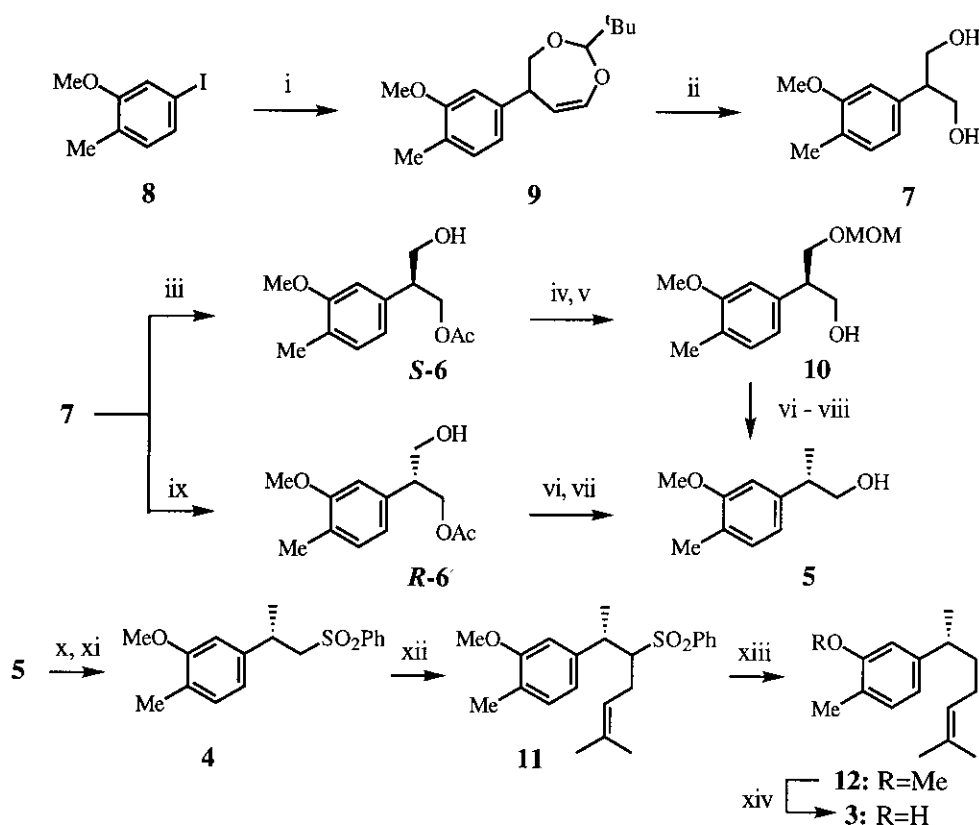
Scheme 2. *Reagents & Conditions*: i, 2-*tert*-butyl-4,7-dihydro-1,3-dioxepine, Pd(OAc)$_2$, Ph$_3$P, ^{i}Pr$_2$NEt, DMF, 80°C, 75%; ii, O$_3$, CH$_2$Cl$_2$:MeOH (1:1), -78°C then NaBH$_4$, rt, 63%; iii, CAL, vinyl acetate, Et$_2$O, rt, 19%; iv, MOMCl, ^{i}Pr$_2$NEt, 4-DMAP, CH$_2$Cl$_2$, rt, 81%; v, LiAlH$_4$, THF, rt; vi, TsCl, Et$_3$N, 4-DMAP, CH$_2$Cl$_2$, 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$_2$O, 39°C, 95%; x, ^{n}Bu$_3$P, Ph$_2$S$_2$, pyridine, rt, 84%; xi, MCPBA, KHCO$_3$, CH$_2$Cl$_2$, rt, 100%; xii, ^{n}BuLi, prenyl bromide, HMPA, THF, -78°C, 82%; xiii, 5% Na-Hg, Na$_2$HPO$_4$, 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**), [α]$_D$ +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 ^nBu3P 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, CHCl3) {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, CHCl3) {lit.,[5] $[\alpha]_D$ -58° (c=1.0, CHCl3)} in 78% yield, whose ^1H-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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