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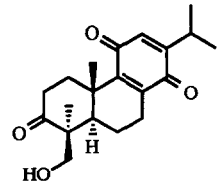
ENANTIOCONTROLLED TOTAL SYNTHESIS OF THE DITERPENOIDS, TRIPTOQUINONE B, C AND TRIPTOCALLOL

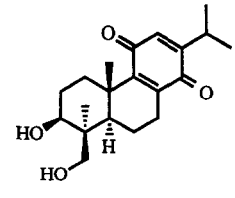
Itsuki Yamamura, Yoko Fujiwara, Toshihiro Yamato,
Osamu Irie and Kozo Shishido*
Institute for Medicinal Resources, University of Tokushima, Sho-machi 1,
Tokushima 770, Japan

Abstract: An efficient and enantiocontrolled synthesis of triptoquinone B and C, which possess interleukin-1 inhibitory activity, has been accomplished employing the lipase-catalyzed kinetic resolution and a highly diastereoselective radical cyclization as key synthetic steps. In addition, the first total synthesis of triptocallol has been achieved utilizing the same strategy.

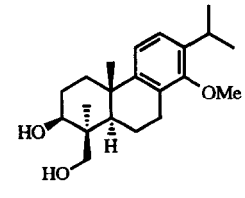
Triptoquinone B **1** and C **2** were isolated from the extracts of the *Tripterygium wilfordii* var. *regelii* together with several related diterpenoids by us.[1] These diterpenoid quinones were found to exhibit a remarkable inhibitory activity on interleukin-1 release and have been expected to be a candidate for treatment of rheumatoid arthritis. Although the total syntheses of **1** and **2** have already been accomplished in a racemic form,[2] the enantiocontrolled syntheses still remain to be explored. In addition, quite recently, triptocallol **3**, which seems to be a biogenetic precursor of **2**, was isolated from the callus of the same plant in a very small amount by Nakano et al.[3] Its potential biological activity and unknown absolute stereostructure have prompted work on the development of an enantioselective and concise synthetic route. In this paper, we report an efficient and enantiocontrolled total synthesis of triptoquinone B **1**, C **2** and triptocallol **3** employing the lipase-catalyzed kinetic resolution[4] and a highly diastereoselective silylmethyl radical cyclization[5] followed by oxidation of the carbon-silicon bond[6] as the key steps for the construction of four contiguous asymmetric stereogenic centers involved in these molecules.



1 triptoquinone B



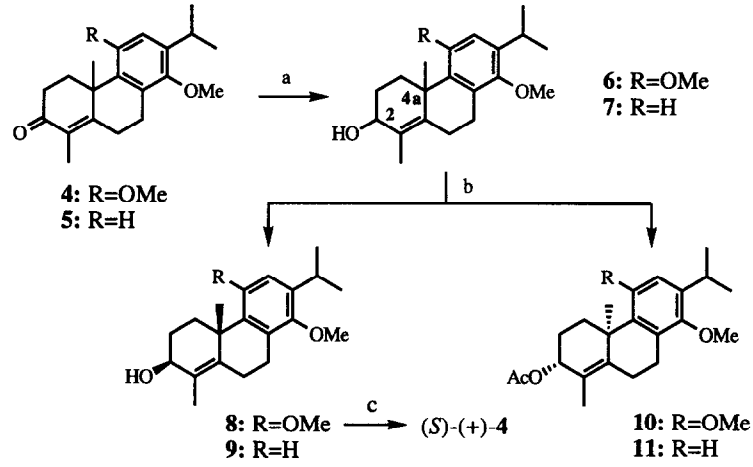
2 triptoquinone C



3 triptocallol

Reduction of the racemic enones **4**, **5**, prepared from 4-bromo-2-isopropylphenol and 2-isopropylphenol by the same sequenc of reactions,[7] with sodium borohydride in the presence of cerium

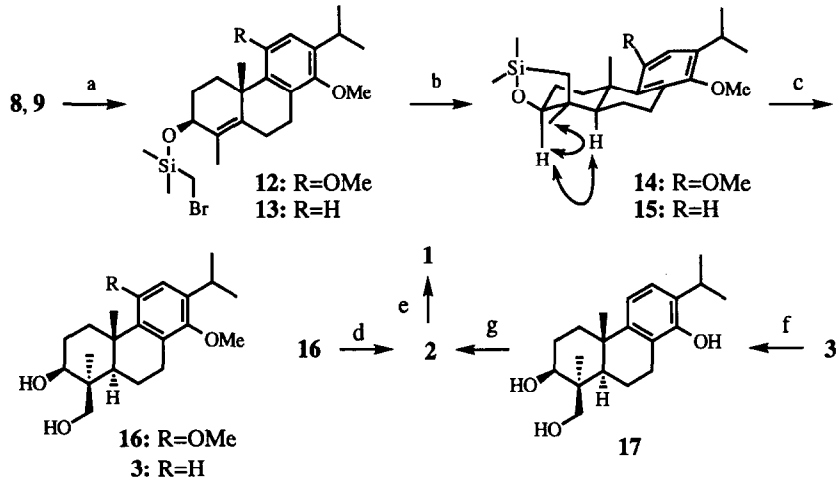
trichloride[8] provided diastereoselectively **6**, **7** in 98% and 81% yields, respectively. The stereochemistry of the racemic allyl alcohols **6**, **7** was deduced to be 2*S* * and 4a*S** from the literature precedent[9] and the ^{1}H-NMR, in which, e.g. for **6**, the quasi-axially oriented α-methine proton at C-2 appears at δ 4.06 as a double doublet with J=6.9 and 9.3 Hz. We next addressed the optical resolution of racemic **6** and **7**, which were found to be suitable substrates for the lipase-catalyzed transesterification[4] with vinyl acetate. An excellent result was obtained with NOVOZYM 435, *Candida antarctica* lipase;[10] only the *R*-alcohols were acetylated, leaving behind the optically enriched alcohols **8**, **9**. The enantiomeric excess (86% ee) and the absolute configuration of **8** were determined upon transformation of **8** into the known optically active enone (+)-**4**[7] by oxidation with PCC. On the other hand, the enatiomeric excess of **9** was 99% as determined by HPLC on a Chiralcel OD column. Although the absolute stereostructure of **9** could not be established at this stage, it was deduced to be the same as that of **8** based on the biogenetic similarity. The confirmation was made eventually by the successful conversion to natural triptoquinone C **2**. (**Scheme 1**)



Scheme 1. ***Reagents & Conditions***: a, $NaBH_4$, $CeCl_3$, MeOH, 98% for **6**, 81% for **7**; b, NOVOZYM 435, vinyl acetate, benzene, 48% and 86% ee for **8**, 41% and 80% ee for **10**, 47% and 99% ee for **9**, 52% and 88% ee for **11**; c, PCC, CH_2Cl_2, 100%.

The optically active **8** and **9** thus obtained were then converted into the bromomethyldimethylsilyl ether **12**, **13**, which were subjected to the catalytic conditions for radical generation[11] to provide the tetracyclic silyl ethers **14**, **15** as a single product via the 5-exo-trigonal mode of cyclization.[5] The structures of both ethers were assigned by ^{1}H-NMR. Using one-dimensional NOE, the configurations at the two newly-generated stereogenic centers were determined as summarized in Scheme 2 in which signal enhancements are indicated by arrows. It should be noted that the examples for the creation of a quaternary stereogenic center by using the Nishiyama-Stork type of radical cyclization are rarely found in the literature.[5c, 12] Treatment of **14** and **15** with hydrogen peroxide and sodium carbonate or potassium hydrogen carbonate[13] produced the 1, 3-diols **16** and **3** in 45% and 52% yield for the 3 steps, respectively. Thus, the crucial construction of four contiguous asymmetric stereogenic centers including two quaternary carbons was achieved. The diol **3**, $[\alpha]_D$+44° (lit.[1] $[\alpha]_D$+43°), thus obtained was completely identical with

natural triptocallol in all respects.[3] According to the procedure developed by us,[2] **16** was then transformed into triptoquinone B **1** and C **2**. Treatment of **16** with ammonium cerium nitrate afforded 86% yield of **2**, which was oxidized chemoselectively with aqueous sodium hypochlorite in acetic acid[14] to give **1** in 89% yield. The spectral properties and optical rotations of synthetic **1**, $[\alpha]_D$+161° (lit.[1] $[\alpha]_D$+167°), and **2**, $[\alpha]_D$-62° (lit.[1] $[\alpha]_D$-63°), were identical with those of natural products. This asymmetric synthesis can equally be applied to synthesis of its enantiomer by switching to *ent*-**8** or **9**, which would be derived easily from **10** or **11**. Finally, in order to determine the absolute structure of **3**, attempted conversion of the synthetic triptocallol **3** into triptoquinone C **2** was examined. Sequential treatment of **3** with ethanethiol/aluminium trichloride[15] and oxidation of the resulting phenol **17** with Fremy's salt $[(KSO_3)_2NO]$[16] produced **2**, $[\alpha]_D$-62°, which was indistinguishable from natural triptoquinone C including the sign of optical rotation.



Scheme 2. ***Reagents & Conditions***: a, $BrCH_2Si(Me)_2Cl$, Et_3N, CH_2Cl_2; b, $NaBH_3CN$, $^nBu_3SnCl$, AIBN, ^{t}BuOH; c, for **14**, Na_2CO_3, H_2O_2, MeOH:THF=1:1, 45% for 3 steps; for **15**, $KHCO_3$, H_2O_2, MeOH:THF=1:1, 52% for 3 steps; d, $(NH_4)_2Ce(NO_3)_6$, aq. CH_3CN, 86%; e, NaOCl, AcOH, 89%; f, EtSH, $AlCl_3$, 72%; g, $(KSO_3)_2NO$, EtOH, KH_2PO_4, MeOH, H_2O, 55%.

In conclusion, the first enantiocontrolled total syntheses of three diterpenoids, triptoquinone B, C and triptocallol, have been accomplished and the absolute stereostructure of triptocallol was found to be the same as that of triptoquinone C. The synthetic route developed here holds considerable promise for the synthesis of other similarly substituted diterpenoids.

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