Enantioselective Synthesis and Absolute Configuration of (+)-Cubitene

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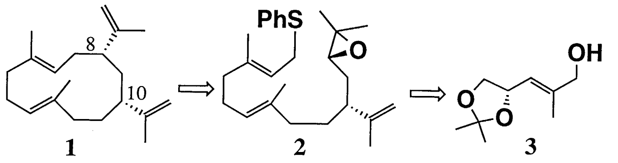
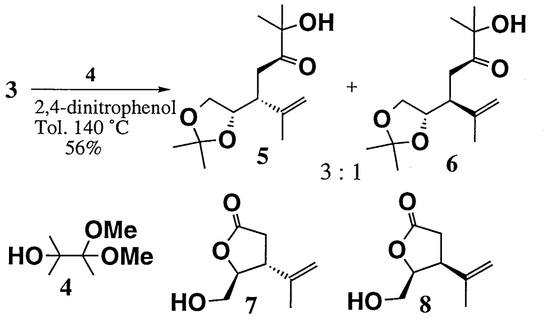
Enantioselective synthesis of (+)-(8*R*,10*R*)-cubitene has been achieved starting from D-mannitol and the absolute configuration of natural cubitene isolated from termites has been determined to be 8*R*, 10*R*.

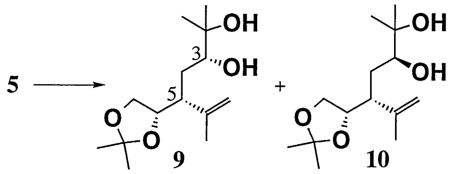
Cubitene is a diterpene hydrocarbon isolated from the defense secretion of East African termites, *Cubitermes umbratus*.[1,2] The novel structure constructed by twelve-membered ring with cis-oriented isopropenyl groups has been established by X-ray crystallographic analysis. However, its absolute stereochemistry has not been clarified for long time. In 1982, we have succeeded the stereoselective synthesis of (±)-cubitene by the intramolecular alkylation of α-sulfenyl carbanion developed by us.[3] In this communication we wish to report the enantioselective synthesis of (8*R*,10*R*)-cubitene (**1**) which was found to be completely identical with natural (+)-cubitene and the absolute configuration of **1** has now been established as 8*R*, 10*R*.

For the construction of twelve-membered ring, we employed the same method used in the synthesis of (±)-**1**, that is, intramolecular reaction of α-sulfenyl carbanion with epoxide. Thus, the target molecule in the present synthesis is the chiral epoxide **2** which would be prepared from the allylic alcohol **3**, readily available from D-mannitol.[4]

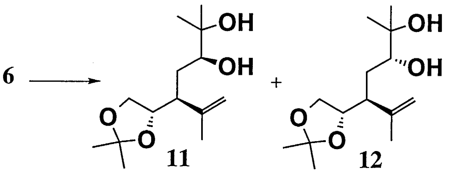


1 **2** **3**





NaBH$_4$	4 : 1	(63%)
DIBAL-H	3 : 1	(96%)
DIBAL-BHT	2 : 1	(69%)
Zn(BH$_4$)$_2$	10 : 11	(100%)
Red-Al	2 : 1	(83%)

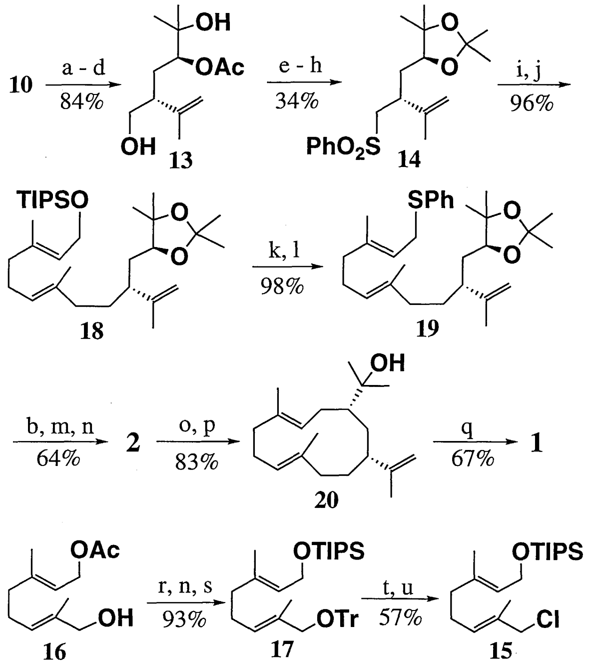


NaBH$_4$ 10 : 1 (68%)

The allylic alcohol **3** was subjected to Claisen rearrangement using the acetal **4**[5] to yield two diastereomeric ketols **5** and **6** in 3:1 ratio in 56% yield. The stereochemistry at newly formed chiral center was determined to be *R* (major **5**) and *S* (minor **6**) by transforming them into the known lactones **7** or **8**.[4] NaBH$_4$ reduction of **5** afforded epimeric alcohols **9**, mp 98-99 °C, and **10**, mp 112-113 °C, in 4:1 ratio in 63% yield, while the minor ketol **6** gave **11** and **12** (10:1) in 68% yield. The configuration at C-3 was unequivocally determined by applying modified Mosher method[6] to the MTPA esters of **9** and **11**.[7] The product in this reduction should have 3,5-*anti* configuration to introduce the cis-oriented isopropenyl groups on the cubitene framework, but the alcohol with desired configuration was found to be a minor product in each reduction. Therefore, various reducing agents were examined to increase the ratio of *anti* product **10** and better result was obtained by zinc borohydride,[8] although the ratio was still limited to ca 1:1.

Acetylation of diol **10**, hydrolysis of acetonide group, cleavage of resulting diol, and reduction of formyl group afforded an alcohol **13** in 84% overall yield. After diol monoacetate part was reprotected by acetonide, the primary alcohol was converted to iodide by Falck's method[9] and then to sulfone to yield **14**, $[\alpha]_D^{25}$ -11.5°. Thus obtained **14** was coupled with the chloride **15**, prepared in 53% overall yield from the allylic alcohol **16**[10] in five-step sequence, to give raise to **18**, $[\alpha]_D^{25}$ -0.7°, after reductive elimination of sulfonyl group in 96% yield. **18** was desilylated and then reacted with diphenyldisulfide in the presence of tri-*n*-butyl phosphine.[11] Modification of the protected diol part of **19** in three-step sequence completed the synthesis of desired epoxy sulfide **2**, $[\alpha]_D^{25}$ -4.4°. The route from **2** to cubitene has already been established in the synthesis of (±)-cubitene. Actually treatement of **2** with *n*-BuLi in the presence of DABCO under high dilution condition yielded twelve-menbered ring alcohol **20** in high yield after reduction of phenylthio group and subsequent dehydration with thionyl chloride followed by AgNO$_3$-impregnated SiO$_2$ chromatography and recrystallization gave (8*R*,10*R*)-cubitene (**1**), mp 32.5-33.0 °C (natural[1]: mp 33.5-34.0 °C).

The optical rotation of synthetic **1** [$[\alpha]_D^{22}$ +88.2° (c 0.27, MeOH[12])] had same sign with that of natural cubitene [$[\alpha]_D$ +128° (*c* 0.76, MeOH[12])]. Thus, the enantioselective synthesis of



a: Ac_2O, Py, DMAP; **b**: *p*-TsOH, THF-H_2O; **c**: $NaIO_4$, THF-H_2O; d: $NaBH_4$, MeOH; **e**: 2M NaOH; **f**: DMP, PPTS; **g**: DEAD, Ph_3P, LiI, DMF; **h**: $PhSO_2Na$, DMF; **i**: 1) *n*-BuLi, THF, 2) **15**; **j**: Na(Hg), MeOH; **k**: *n*-Bu_4NF; **l**: PhSSPh, Ph_3P; **m**: MsCl, Py, DMAP; **n**: K_2CO_3, MeOH; **o**: *n*-BuLi, DABCO, THF; **p**: Na, *n*-BuOH; **q**: $SOCl_2$,Py; **r**: TrCl, Et_3N; **s**: TIPS-Cl, imidazole, DMF; **t**: HCOOH, ether; **u**: DEAD, Ph_3P, LiCl

(+)-cubitene has been achieved and the absolute stereostructure of natural cubitene was determined as **1**.

References and Notes

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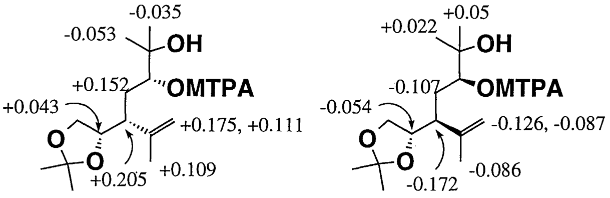
7 $\Delta\delta(=\delta_S - \delta_R)$ values of MTPA esters of 9 and 11 :



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12 The solvent, methanol, used for the measurement of optical rotation contains a small amount of hexane.