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STEREOSELECTIVE EPOXYDATION OF 1-IRIDENE DERIVATIVES. TOTAL SYNTHESES OF METHYL CHOKOLATE A AND MATATABIETHER

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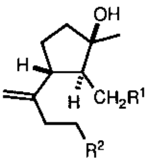
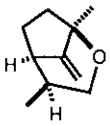
Abstract——Sharpless oxidation of 1-iridenes stereoselectively afforded trans-epoxy derivatives. As expected, the selectivity was inversed to give cis-epoxy derivatives when 1-iriden-9-ols were similarly treated. The trans- and cis-epoxy derivatives, thus obtained, were converted into optically active methyl chokolate A and matatabiether, respectively.

1-Iridene derivatives are important synthons for higher terpenoids as have been demonstrated in our syntheses of several 5-8-5-membered tricyclic higher terpenoids, such as cycloaraneosene,[1,2] hydroxycycloaraneosene,[1,3] ceroplastol II,[4,5] and albolic acid,[5,6] as well as dictymal,[7,8] a biogenetically-linked seco-derivative of such a tricyclic diterpenoid, epoxydictymene.[9] In order to make iridanes more versatile for higher terpenoids syntheses, it is desirable to develop stereoselective method of introducing oxygen functions into certain positions of iridanes.



Chokol A
$R^1 = H$, $R^2 = CH_2OH$
Methyl chokolate A (**1**)
$R^1 = OH$, $R^2 = CO_2Me$



Matatabiether (**2**)

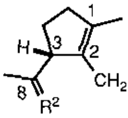
Herein, we will show a highly stereoselective epoxidation of 1-iridene derivatives by Sharpless oxidation[10] leading to total syntheses of methyl chokolate A (**1**),[11] a fungitoxic trisnorsesquiterpenoid co-metabolite of chokols A–G isolated from stroma of the timothy Phleum pratense infected by

Epichloe typhina,[12] and matatabiether (**2**), a monoterpenoid ether from *Actinidia polygama*.[13]

First of all, when 1,8-iridadien-7-ol (**3**)[2] was epoxidized under Sharpless oxidation conditions, and after acetylation, two isomeric epoxides (**4** and **5**) were obtained in 86 and 10% yields, respectively. Similarly, the epoxidation of 9-benzyloxy-1-iriden-7-ol (**6**) gave two epoxy derivatives (**7** and **8**) in 84 and 5% yields, respectively. The major products **4** and **7** should have trans orientation to the bulky C_3-side chains in **3** and **6**.

On the other hand, 1-iriden-9-ol derivatives afforded cis-epoxy derivatives; i.e., the Sharpless oxidation of 7-(t-butyl)dimethylsilyloxy-1-iriden-9-ol (**9**) gave a sole epoxy acetate (**10**) in 76% yield after acetylation of the product.

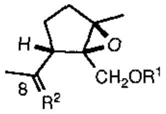
As predicted, epoxidation with m-chloroperbenzoic acid proceeded less stereoselectively; e.g., **6** gave two epoxy alcohols (**11**, 78% and **12**, 20%), and acetates derived from **11** and **12** were identical with **7** and **8**, respectively. On the other hand, **9** gave two epoxy alcohols (**13**, 37% and **14**, 20%), and two secondary products (**15**, 23% and **16**, 6%). An acetylation of **14** gave **10**, while a mild acid treatment of **13** with pyridinium p-toluenesulfonate (PPTS)[14] in THF gave **15** (86%) and **16** (14%). Therefore, the stereochemistries, cis for **10** and **14**, and trans for **13**, were unambiguously assigned.



3 : $R^1 = H$, $R^2 = CH_2$

6 : $R^1 = H$, $R^2 = 8\beta\text{-}H, CH_2OBn$

9 : $R^1 = Si(Me)_2{}^tBu$, $R^2 = 8\beta\text{-}H, CH_2OH$

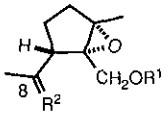


4 : $R^1 = Ac$, $R^2 = CH_2$

7 : $R^1 = Ac$, $R^2 = 8\beta\text{-}H, CH_2OBn$

11 : $R^1 = H$, $R^2 = 8\beta\text{-}H, CH_2OBn$

13 : $R^1 = Si(Me)_2{}^tBu$, $R^2 = 8\beta\text{-}H, CH_2OH$



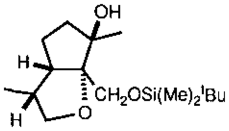
5 : $R^1 = Ac$, $R^2 = CH_2$

8 : $R^1 = Ac$, $R^2 = 8\beta\text{-}H, CH_2OBn$

10 : $R^1 = Si(Me)_2{}^tBu$, $R^2 = 8\beta\text{-}H, CH_2OAc$

12 : $R^1 = H$, $R^2 = 8\beta\text{-}H, CH_2OBn$

14 : $R^1 = Si(Me)_2{}^tBu$, $R^2 = 8\beta\text{-}H, CH_2OH$



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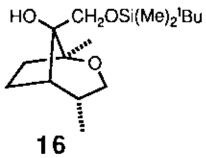

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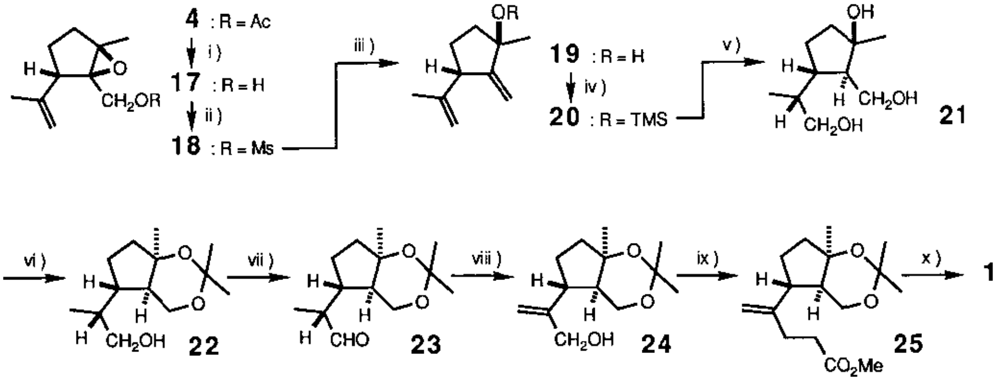
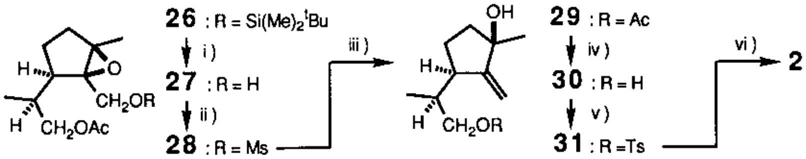
The trans- and the cis-epoxy derivatives thus obtained were employed in stereoselective synthesis of optically pure methyl chokolate A (**1**) and matatabiether (**2**) as follows: The (1R,2R,3S)-trans-epoxide **4** was deacetylated by LAH reduction to an epoxy alcohol **17**, whose methanesulfonylation gave an epoxy mesylate **18**. Treatment of **18** with Zn-NaI in DMF afforded a dehydrocyclolinalool, 2(7),8-iridadien-1-ol (**19**),[15] which was, after being converted into a trimethylsilyloxy ether **20**, hydroborated with thexylborane to give triol **21** after mild deprotection of trimethylsilyl group with PPTS in THF. Acetone dimethylacetal treatment of **21** with PPTS in CH_2Cl_2 afforded a 1,3-dioxolane derivative **22** which stereostructure was deduced as depicted from NOE experiments. An oxidation of **22** gave an aldehyde **23**, which was further converted into an allyl alcohol **24** via consecutive treatment with $CF_3SO_3SiMe_3$ and Et_3N in CH_2Cl_2, $Pd(OAc)_2$-oxidation in MeCN[16] and $NaBH_4$ reduction in the presence of $CeCl_3$ in MeOH.[17] The oxa-Claisen rearrangement[18] of 1-methyloxyethenyl ether of **24** gave a compound **25**, corresponding to a dimethyl acetal derivative of **1**. Synthetic compound obtained by hydrolytic deprotection of **25** was identical with natural **1**[11] in respect of ^{1}H- and ^{13}C-nmr as well as ir spectral comparisons.[19] Currently, a considerable attention has been paid for these biologically active metabolites: Although chokol A[12] has been synthesized by several workers,[20] this is the first total synthesis of **1**.



i) $LiAlH_4$ / THF, 90% ; ii) MsCl / Py, 95% ; iii) Zn, NaI / DMF, 68% ; iv) TMSCl / Py, 79% ; v) $Me_2CHCMe_2BH_2$; H_2O_2 ; PPTS / aq. THF, 75% ; vi) $Me_2C(OMe)_2$, PPTS / CH_2Cl_2, 67% ; vii) PCC / CH_2Cl_2, 55% ; viii) CF_3SO_3TMS, Et_3N / CH_2Cl_2 ; $Pd(OAc)_2$ / MeCN ; $NaBH_4$, $CeCl_3$ / MeOH, 10% ; ix) $MeC(OMe)_3$, $EtCO_2H$ / xylene, 80% ; x) PPTS / aq. THF, 73%

Then, (1R,2R,3R)-cis-epoxy derivative **26** (the enantiomer of **10**) was desilylated with Bu_4NF to an epoxy alcohol **27** and mesylated to **28**, which, upon

Zn-NaI reduction in DMF, afforded 9-acetoxy-2(7)-iriden-1-ol (**29**). A glycol, 2(7)-iridene-1,9-diol (**30**), obtained by LAH-reduction of **29**, was tosylated with p-toluenesulfonyl chloride in pyridine to give a mono-tosylate **31**. A sodium hydride treatment of **31** in DMF gave an ether which was identical with matatabiether (**2**) in every respect. Since **2** has been obtained by chemical transformations during structure study,[13] the present result is an alternative synthesis of **2**.



i) Bu_4NF / THF, 92% ; ii) MsCl / Py, 95% ; iii) Zn, NaI / DMF, 84% ; iv) $LiAlH_4$ / THF, 98% ;
v) TsCl / Py, 90% ; vi) NaH / DMF, 80%

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