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Stereospecific Total Synthesis of Dimorphecolic Acid, 5(S)-HETE, and 12(S)-HETE

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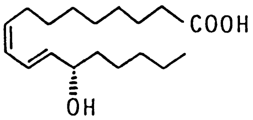
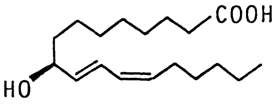
First enantiospecific synthesis of dimorphecolic acid is accomplished via an efficient and stereocontrolled route. The convenient synthesis of 5(S)-HETE and 12(S)-HETE is also described.

Recently various lipoxygenase metabolites of linoleic acid have been isolated from biological systems. Among them, coriolic acid (1) and dimorphecolic acid (2) isolated from the resistant cultivar of rice plant Fukuyuki (Oryza sative L.) were demonstrated to act as self defensive substances against rice blast disease.[1] These products 1 and 2 were also isolated from bovine heart mitochondria[2] and sera of patients with familial Mediterranean fever[3] and shown to possess cation-specific ionophoric activity. Because of the low availability of these compounds from natural sources, their total syntheses have attracted much interests for further biological investigations. Although synthesis of optically active 1 has been accomplished by several groups including us,[4] synthesis of optically active 2 has not been reported.[5] We have now succeeded in a first enantiospecific total synthesis of 2 via an efficient and stereocontrolled route, and confirmed that 2 isolated from the rice plant exists as a mostly racemic mixture in which the (S)-enantiomer is predominant.



Coriolic acid (1)

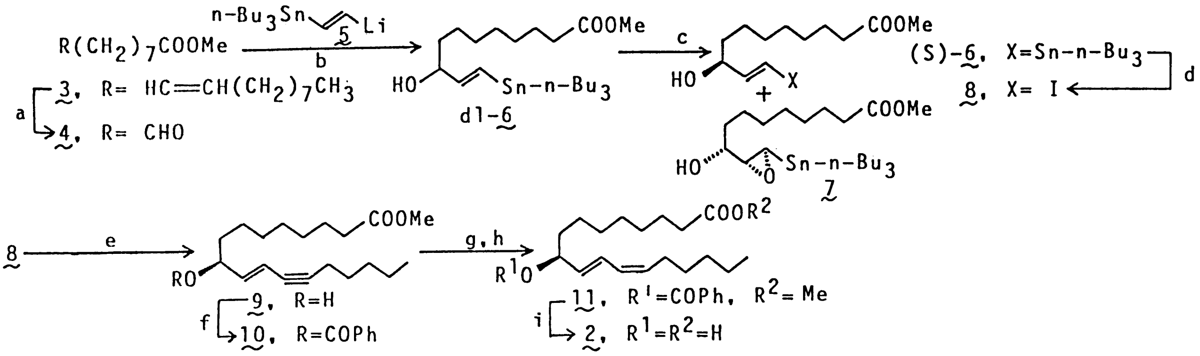


Dimorphecoric acid (2)

Our synthesis of 2 is delineated in Scheme 1. The optically pure key intermediate 8 is prepared unambiguously based on our recently reported general approach to optically pure γ-iodo allylic alcohols in which the Sharpless kinetic resolution plays a central role,[6] and the cis, trans diene unit of 2 is constructed from 8 and 1-heptyne according to the Nicolaou's method for synthesis of lipoxygenase metabolites of arachidonic acid which employs the Cu^{I}-Pd^{0} coupling reaction.[7]

Ozonolysis of methyl oleate (3) produced after Me$_2$S work up the aldehyde 4 which was reacted with the anion 5[8] to afford dl-6 in 35% yield. Kinetic resolution of dl-6 was carried out by using t-butyl hydroperoxide (TBHP) (1.5

equiv.), D(-)DIPT (0.36 equiv.), and Ti(O-i-Pr)$_4$ (0.30 equiv.) in CH_2Cl_2 at -21 °C for 36 h to afford a mixture of the alcohol (S)-6 and the epoxide 7,[6d] which, without separation, was treated with I_2 in Et_2O to produce the key intermediate 8 (>99% ee, $[\alpha]_D^{25}$ +3.75 (c 2.24, $CHCl_3$))[9] in 40% yield from dl-6 (80% of theory) after column chromatography on silica gel. Coupling reaction of 8 and 1-heptyne in the presence of catalytic amounts of $Pd(PPh_3)_4$ and CuI in n-$PrNH_2$-PhH afforded the alcohol 9, which was converted into the benzoate 10 (96% yield from 8).[7] cis-Reduction of 10 into 11 was accomplished in 73% yield by hydroboration using $(Sia)_2BH$ (1.5 equiv., THF, 0 °C, 1 h) followed by protonolysis (AcOH (5 equiv.), 40 °C, 2 h) and oxidative work up (H_2O_2 (4 equiv.), NaOH (3 equiv.), 0 °C, 15 min, Et_2O). Finally, hydrolysis of 11 yielded 2 in 95% yield. The spectroscopic data (^1H and/or ^{13}C NMR) of 11 and 2 were identical with those of the literatures.[1,5] Comparison of the specific rotation of 11 thus synthesized ($[\alpha]_D^{25}$ +69.2° (c 1.00, $CHCl_3$)) with that derived from naturally ocurring 2 ($[\alpha]_D^{20}$ +2.2 (c 1.86, $CHCl_3$))[1] revealed that the compound 2 derived from the rice plant has (S)-configuration as suggested by Kato et al. based on its possitive CD curve[1] and consists of a mostly racemic mixture.

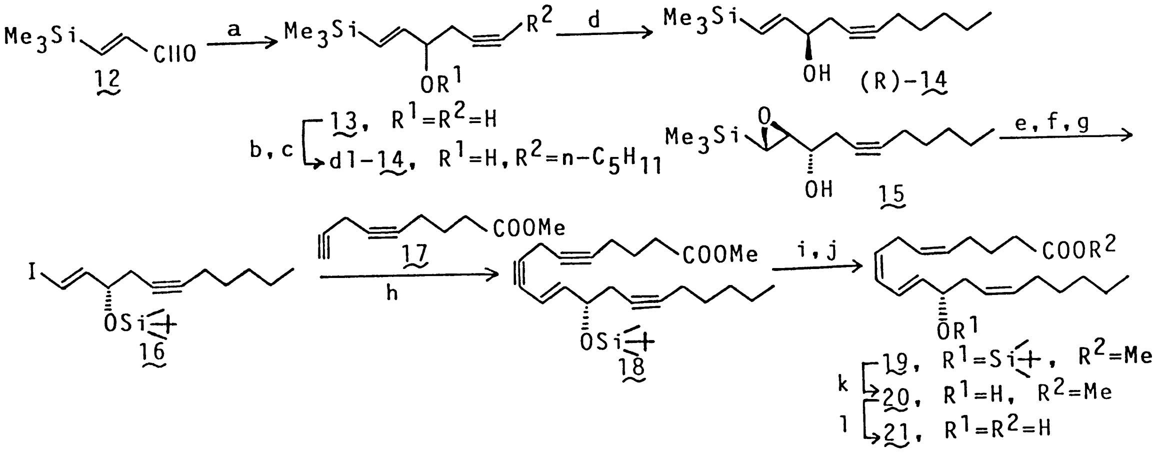


a, O_3, MeOH, CH_2Cl_2, C_5H_5N; b, 5, THF, -78 °C; c, TBHP, Ti(O-i-Pr)$_4$, D(-)DIPT, CH_2Cl_2, -21 °C; d, I_2, Et_2O; e, 1-heptyne, $Pd(PPh_3)_4$ (cat.), CuI (cat.), n-$PrNH_2$, PhH; f, PhCOCl, C_5H_5N; g, $(Sia)_2BH$, THF, 0 °C then AcOH, 40 °C, 2 h; h, H_2O_2, NaOH, 0 °C; i, LiOH, DME-H_2O.

Scheme 1.

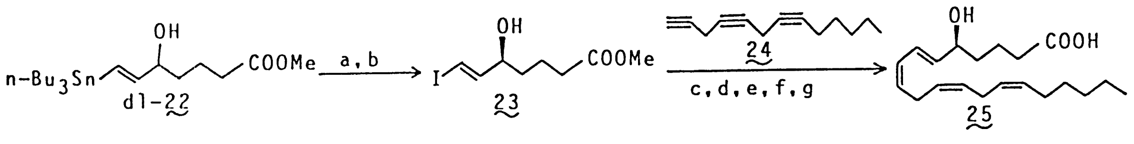
The present method for synthesis of 2 is apparently applicable for synthesis of hydroxyeicosatetraenoic acids (HETEs) which are monohydroxylated metabolites of arachidonic acid and have been shown to play a central role in inflammation and a number of other health-problems.[10] In the remaining paragraph, we describe the synthesis of 12(S)-HETE and 5(S)-HETE.[11]

Scheme 2 shows the synthesis of 12(S)-HETE (21). Reaction of the aldehyde 12[12] and propargyl bromide (Zn-dust (2 equiv.) and $TiCl_4$ (0.005 equiv.), THF, 0 °C) afforded 13[13] quantitatively. The ethoxyethyl ether of 13 was alkylated with n-$C_5H_{11}Br$ to afford dl-14 after hydrolysis in 77% yield from 13. Kinetic resolution of dl-14 using TBHP, Ti(O-i-Pr)$_4$, and L(+)DIPT afforded the epoxide 15 (>99% ee)[9] and (R)-14 (>99% ee)[9] in 82% and 84% yields of theory,



a, $HC{\equiv}CCH_2Br$, Zn, $TiCl_4$ (cat.); b, $CH_2{=}CHOEt$, H^+; c, $n\text{-}C_5H_{11}Br$, n-BuLi, THF-HMPA then H^+; d, TBHP, $Ti(O\text{-}i\text{-}Pr)_4$, L(+)DIPT; e, $n\text{-}Bu_3SnLi$; f, I_2, Et_2O; g, $t\text{-}BuMe_2SiCl$; h, 17, $Pd(PPh_3)_4$ (cat.), CuI (cat.); i, $(Sia)_2BH$, THF, then AcOH; j, H_2O_2, NaOH; k, $n\text{-}Bu_4NF$; l, LiOH.

Scheme 2.



a, TBHP, $Ti(O\text{-}i\text{-}Pr)_4$, D(−)DIPT; b, I_2, Et_2O; c, $t\text{-}BuMe_2SiCl$; d, 24, $Pd(PPh_3)_4$ (cat.), CuI (cat.); e, $(Sia)_2BH$, THF then AcOH; f, H_2O_2, NaOH; g, $n\text{-}Bu_4NF$.

Scheme 3.

respectively.[6a,b] By using the reported procedure,[6c] 15 was converted into the iodide 16 in 84% overall yield. Coupling reaction of 16 and the diyne 17[14] ($CuI\text{-}Pd(PPh_3)_4\text{-}n\text{-}PrNH_2$) and cis-reduction of the resulting 18 via hydroboration furnished 19 in 73% yield.[15] Deprotection of 19 afforded 20 ($[\alpha]_D^{22}$ +12.0° (c 1.0, acetone); lit.[11b] $[\alpha]_D^{22}$ +13° (c 1.5, acetone)) which upon hydrolysis gave 21 (>95% pure by RP-HPLC analysis) in 79% yield.

In a similar manner, 5(S)-HETE (25) (>95% pure by RP-HPLC analysis) was synthesized (Scheme 3) starting with the optically pure iodide 23 (>99% ee, 55% yield from 23)[9] which was prepared by the kinetic resolution of the racemic alcohol dl-22 followed by treatment with I_2 (88% yield of theory).[6d] The optical rotation of methyl ester of 25 ($[\alpha]_D^{23}$ +14.2° (c 1.96, PhH)) is in good agreement with the reported one ($[\alpha]_D^{23}$ +14.4 (c 2.0, PhH)).[11a]

Although our present approach to 21 and 25 is essentially the same one as that reported by Nicolaou,[7a] in our case, however, the optically pure intermediates 16 and 23 are employed thus leading to the corresponding homochiral HETEs (21 and 25), respectively.

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15) Catalytic hydrogenation of **18** (Pd/$BaSO_4$, quinoline, MeOH) was found to give a considerable amount of unidentified product(s) in addition to the desired product **19**.

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