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C-H INSERTION METHOD FOR THE CHIRAL TERTIARY ALCOHOL: FORMAL SYNTHESIS OF (-)-FRONTALIN

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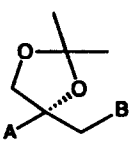
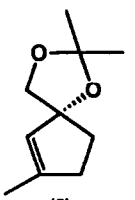
Abstract: Intramolecular insertion of the alkylidene carbene into C-H bond adjacent to the protected secondary hydroxyl group gave a chiral tertiary alcohol derivative, which was converted to a synthetic intermediate of (-)-frontalin.

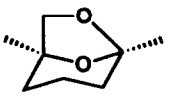
A type of compound (1) (A, B = different functional groups) is adapted as a versatile chiral building block for the synthesis of natural products in which a chiral tertiary alcohol is incorporated, such as frontalin, malyngolide, 4-demethoxydaunomycinone and so on.[1]. Described here is preparation of the compound (2), which can be regarded as structure (1), utilizing the intramolecular C-H insertion reaction of the alkylidene carbene.[2] Compound 2 was converted to the synthetic intermediate of (-)-frontalin (3),[1a] an aggregation pheromone of the southern pine beetle.



(1) A, B= functional group



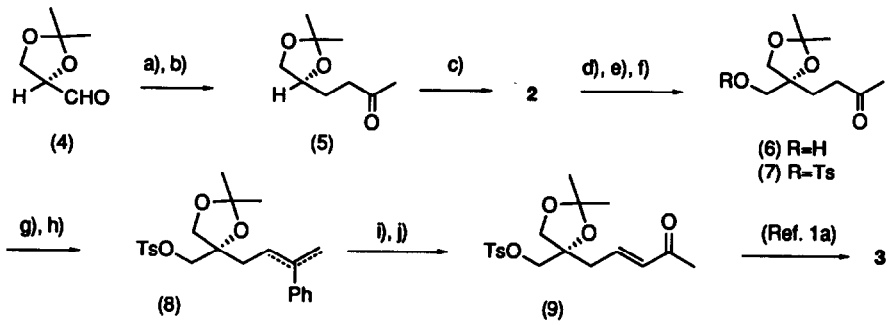
(2)



(3)

D-Glyceraldehyde (4) was treated with dimethyl (2-oxopropyl)phosphonate and potassium carbonate, followed by hydrogenation over 10% Pd/C to give the saturated ketone (5) in high yield.[3] Wittig-Horner type olefination of 5, generation of the alkylidene carbene and subsequent intramolecular C-H insertion proceeded cleanly with dimethyl (diazomethyl)phosphonate[4] in the presence of potassium t-buthoxide in THF at -78°C, affording compound (3) ($[\alpha]_D$= +13.1° (c=1.33, $CHCl_3$)[5] in 68% yield as a single product. The enatiomeric excess of 2 was determined on the way to the formal synthesis of (–)-3.

The double bond of 2 was cleaved under Lemieux-Johnson's conditions and the resulting keto aldehyde was selectively reduced with tetra-n-butylammonium triacetoxyborohydride[6] to keto alcohol (6) ($[\alpha]_D$ = -5.8° (c=0.89, $CHCl_3$)). The NMR analysis of the corresponding MTPA ester confirmed 92% ee of 6. We assume that partial racemization may have occurred at the first step (Wittig-Horner reaction of 4), because over 99% inversion of stereochemistry was observed in the related reaction.[2d] After p-toluenesulfonylation



a) $(MeO)_2POCH_2COMe$, K_2CO_3, THF-H_2O, O°C, 1h ,97%; b) H_2, Pd/C, 91%; c) $(MeO)_2POCHN_2$, t-BuOK,THF, -78°C, 5h, 68%; d) 5mol% OsO_4, $NaIO_4$, THF-H_2O, rt, 5h; e) n-$Bu_4NBH(OAc)_3$, CH_2Cl_2, rt, 7h, 61% from 3; f) TsCl, Py, rt, 71%; g) PhMgBr, Et_2O, 0°C, 1h; h) $POCl_3$, Py, 50°C, 3h, 41% from 7; i) O_3, CH_2Cl_2-MeOH; Me_2S; j) ($MeO)_2POCH_2COMe$, K_2CO_3, THF-H_2O, O°C, 32% from 9

of **6**, two carbon degradation was achieved in three steps: addition of phenylmagnesium bromide to the tosylate (**7**), followed by dehydration, and ozonolysis of the resulting 1:1 mixture of olefins (**8**). Reaction of the crude aldehyde and dimethyl (2-oxopropyl)phosphonate gave the known compound (**9**) ($[\alpha]_D$= - 8.1° (c=1.04, $CHCl_3$), lit.: - 8.5°; mp 68.5 - 69.0°C, lit.: 68°C).[7]

Characteristic point of this synthetic pathway is that three carbons of the target molecule originate from one of the most common chiral building blocks (**4**), and all of the rest from the common reagent dimethyl (2-oxopropyl)phosphonate, since dimethyl (diazomethyl)phosphonate was prepared from the latter compound.[4b]

Approaches to the other natural products using the reaction of alkylidene carbene as a key step are now under investigation.

References and Notes

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5) ^{1}H-NMR ($CDCl_3$ 400 MHz) δ 5.31-5.33 (m, 1H), 3.85 (s, 2H), 2.39-2.47 (m, 1H), 2.04-2.23 (m, 3H), 1.77 (bs, 3H), 1.40 (s, 3H), 1.39 (s, 3H); IR ($CHCl_3$) ν 1658, 1051 cm^{-1}; MS m/e (rel intensity) 168 (0.5, M^+), 153 (14), 110 (100), 93 (95), 72 (95).

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7) We thank Professor C. Monneret of Institut Curie, Paris, for providing us with spectral data of his synthetic intermediate of (-)-frontalin.

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