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SYNTHESIS OF (S)-(+)-2-tert-BUTYL-2-METHYL-1,3-BENZODIOXOLE-4-CARBOXYLIC ACID: A NEW TYPE CHIRAL DERIVATION REAGENT FOR AMINES AND ALCOHOLS

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Summary: A new chiral derivation reagent was developed for chiral amines and alcohols to determine the absolute configuration by circular dichroism and optical purity by ^{1}H-NMR and liquid chromatography.

Several chiral derivation reagents like MTPA[1], GITC[2] and FLEC[3] and HPLC chiral stationary phases[4] have been proposed to determine the optical purity of chiral amines and alcohols with a liquid chromatography (LC) or neclear magnetic resonance (NMR) spectroscopy. On the other hand, circular dichroic (CD) spectroscopy provides an exciton chirality method to determine the absolute configuration of chiral alcohols and amines after they are derived with suitable chromophores like p-substituted benzoates.[5] In this study, we wish to report a new chiral derivation reagent with a benzoic acid skeleton, (S)-(+)-2-tert-butyl-2-methyl-1,3-benzodioxole-4-carboxylic acid [(+)-TBM] which is expected to be useful for the simultaneous determination of the absolute configuration by CD and the enantiomeric excess by ^{1}H-NMR or LC analysis.

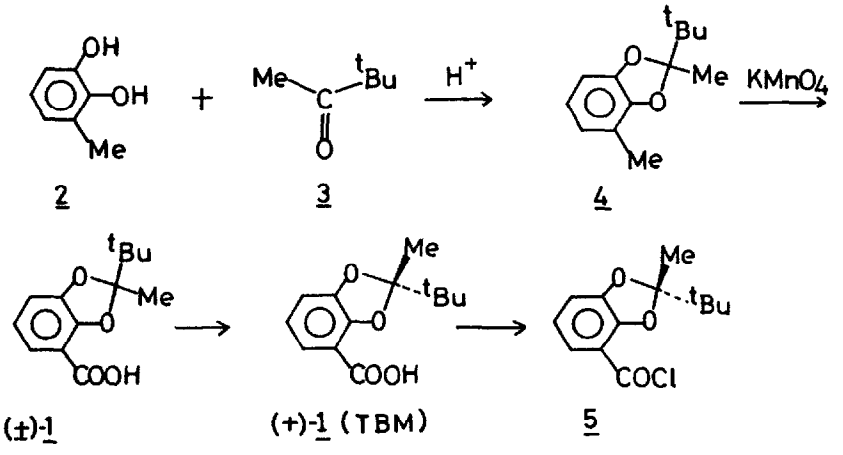
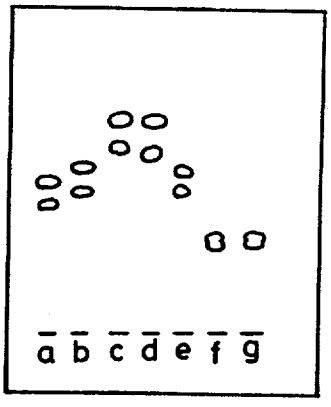


Fig. 1 Preparation of (+)-TBM Reagent [(+)-1].

(+)-TBM was synthesized from commercially available 2,3-dihydroxytoluene (2) and tert-butylmethyl ketone (3 in Fig. 1). Condensation between 2 and 3 in the presence of p-tolunesulfonic acid (refluxed with toluene for 64 hr) gave a crystalline (±)-2-tert-butyl-2,4-dimethyl-1,3-benzodioxole (4) (mp = 27 ℃, 80% yield based on the amount of 2). Oxidation of 4 with $KMnO_4$ in a pyridine-water mixture (1:1) (70-80 ℃ for 6 hr) gave a racemic TBM (mp = 179-180 ℃) in a 65% yield, which was optically resolved with cinchonidine to give a desired (+)-TBM with >98% e.e. (^{1}H-NMR analysis of an L-phenylalanine derivative, Fig. 3). Its absolute configuration was determined by a X-ray crystallographic analysis of the L-phenylalanine derivative to be a 2S-configuration.[6]

(+)-TBM: mp = 176.5-177 ℃, $[\alpha]_D$ +30.7° (c 0.4, MeOH), CD : $[\theta]$max = +1800 (318nm), UV : ε =16600 (218nm), 6000 (shoulder band at ca. 235nm), 4000 (315nm).

The cyclic ketal in (+)-TBM was very stable, and it turned out that the reagent was stable without any decomposition and racemization for 6 months at room temperature. Its treatment with thionyl chloride in benzene gave an acid chloride 5 quantitatively, which is used for the derivation of amines and alcohols in pyridine.



Silica gel TLC (HPLC plate, Kieselgel 60F$_{254}$ (MERCK))
Solvents: n-hexane:ethyl acetate = 3:1
Detection: UV lamp
Compounds; a = (+)-TBM-L-Methionine methyl ester
b = (+)-TBM-L-Alanine methyl ester
c = (+)-TBM-L-Isoleucine methyl ester
d = (+)-TBM-L-Leucine methyl ester
e = (+)-TBM-L-Phenylalanine methyl ester
f = (+)-TBM-L-Aspartic acid methyl ester
g = (+)-TBM-L-Glutamic acid methyl ester

Fig. 2 TLC Separations of TBM-Amino Acid Diastereomers.

Using several L-amino acid methyl esters, an applicability of this reagent as a chiral resolving agent was tested (Fig. 2). Consequently, we found that diastereomers of (±)-TBM-L-amino acids studied here were well separated on a silica gel TLC (Fig. 2) and on a usual silica gel column chromatography in preparative scale (gram scale). The reagent itself and its alcohol or amine derivatives have a visible (blue) fluorescence (Ex. 310 nm, Em. 380 nm) by which highly sensitive LC (HPLC or TLC) determinations of the optical purity and/or absolute configuration of chiral amines and alcohols will become feasible with this reagent.

^{1}H-NMR spectroscopy is an alternative method to determine the optical purity of chiral compounds. ^{1}H-NMR spectra of (+)- and (-)-TBM-L-phenylalanine methyl esters showed that singlet peaks of both of tert-butyl and methyl groups of TBM were well separated between the two diastereomers. The other TBM-amino acids studied here showed similar separations to indicate that ^{1}H-NMR chemical shifts and intensities of the two isolated methyl signals of the reagent will be used to determine the optical purity or absolute configuration of chiral amines and alcohols.

UV spectrum of (+)-TBM in MeOH gave a strong $\pi-\pi^*$ absorption band at ca. 220 nm and weaker bands at 235 mn and 315 nm. Its CD spectrum gave a band at ca. 320 nm ($[\theta]$=+1600), while CD bands below 240 nm were ambiguous because of the strong UV absorption in this region and inherently low intensity of CD ($|[\theta]|<3000$). For CD analyses based on the exciton chirality method,[5] the transition band at ca. 220 nm seemed to be effective. Methyl 3-O-benzoyl-2-O-(+)TBM-β-D-glucopyranoside and methyl 2-O-benzoyl-3-O-(+)TBM-β-D-galactopyranoside with a positive chirality between C2-OR and C3-OR bonds (Fig. 4) gave clear couplet CD peaks, the positive sign of which accorded with a dibenzoate chirality rule.[5] Two asymmetric allylic alcohols with a 4S-configuration (E and Z isomers) derived with a racemic TBM gave positive exciton couplet peaks centered at ca. 220 nm to reflect their 4S-configuration, and this result accorded with the acyclic allylic benzoate chirality rule[7] which was extended to the conjugated diene systems[8]. *The CD bands of (+)-TBM itself were negligibly small compared*

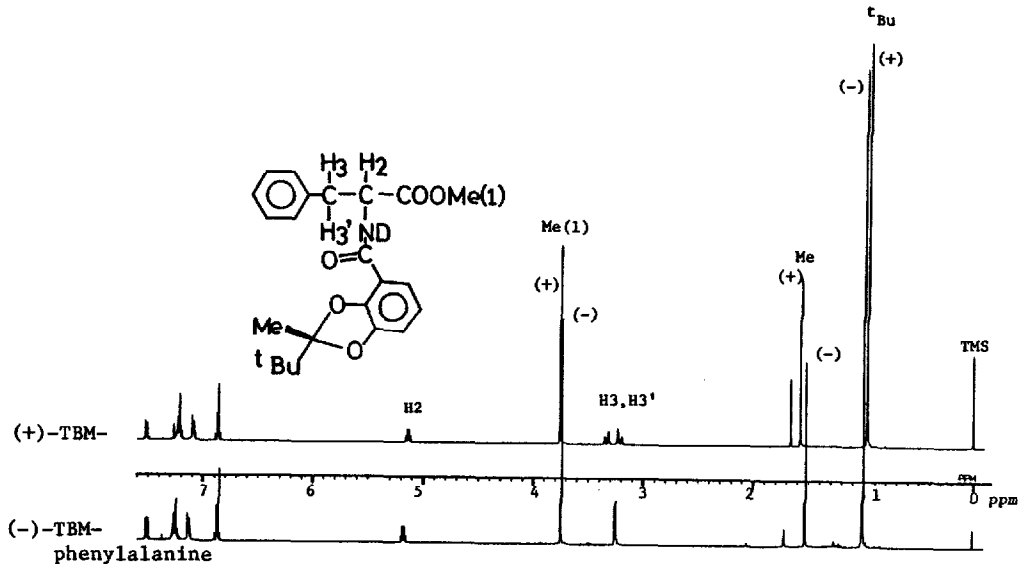


Fig. 3 400 MHz ^{1}H-NMR Spectra of (+)- and (-)-TBM-L-phenylalanine Derivatives in $CDCl_3$.

with the exciton couplet CD peaks. All these results showed that this reagent was useful as a CD chromophore to determine the absolute configuration of asymmetric diols or diamines and allylic alcohols. Further experimental approach will be continued to establish its utility for the CD, NMR and LC analyses of chiral amines and alcohols.

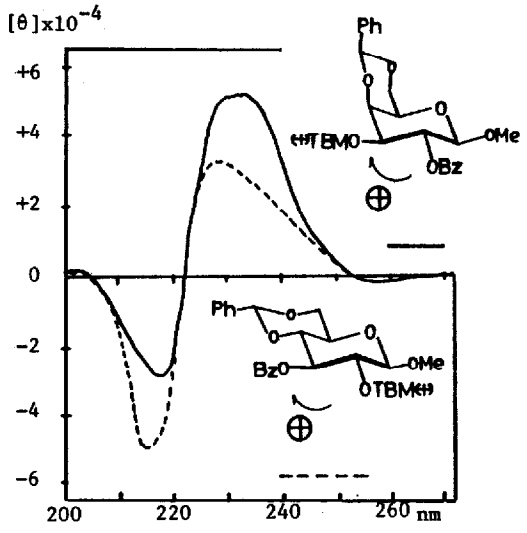


Fig. 4 CD Spectra in EtOH Solution.

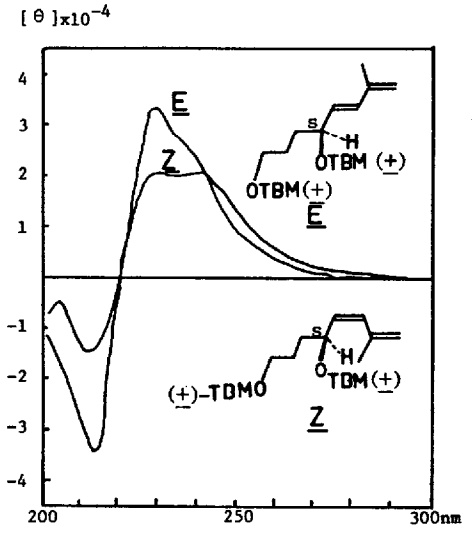


Fig. 5 CD Spectra in MeOH Solution.

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