Tetrahedron: Asymmetry Vol. 4, No. 7, pp. 1431-1434, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

(+)-*Tert*-BUTYL-1,3-BENZODIOXOLE-4-CARBOXYLIC ACID: FLUORESCENT CHIRAL CARBOXYLIC ACID WITH A 1,3-BENZODIOXOLE SKELETON

Yoshihiro Nishida, Masayuki Abe, Hiroshi Ohrui and Hiroshi Meguro

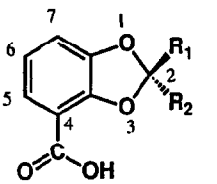
Department of Applied Biological Chemistry, Faculty of Agriculture, Tohoku University, Tsutsumidohri-Amamiyamachi 1-1, *Sendai 981*, JAPAN.

(*Received in Japan* 19 *March* 1993)

Summary: A new chiral carboxylic acid was prepared from catechol *via* acetal formation with trimethylacetaldehyde and trimethylsilyl chloride followed by carbonation with *n*-BuLi and solid CO_2

Several chiral carboxylic acids have been used as chiral derivatizing agents to determine the optical purity and the absolute configuration of alcohols and amines.[1-5] Previously, we reported a new type of chiral carboxylic acid, (*S*)-(+)-TBMB carboxylic acid (1, Fig. 1) with a 1,3-benzodioxole skeletone.[6] The acid has a stereogenic center at the C-2 position bearing two alkyl groups (*tert*-butyl and methyl) and two oxygens (O-1 and O-3) which are unequivalent to each other due to the carboxylic acid at the C-4 position. The acid has several advantages as a chiral derivatizing agent.[6,7] For example, the acid, its esters and amides are fluorescent; this enables selective and sensitive detection of the derivatives on TLC or HPLC separation. Moreover, the agent acts as a benzoate chromophore in the CD (circular dichroism) analysis to elucidate the absolute configuration.[8]

The acid (+)-1 was prepared from 3-methylcatechol *via* a ketal formation with *tert*-butylmethylketone followed by $KMnO_4$ oxidation at the benzylmethyl moiety into carboxylic acid.[6a] The synthetic approach implies that the use of the other dissymmetric ketones or aldehydes instead of *tert*-butylmethyl ketone would enable us to design and prepare a variety of chiral carboxylic acids with the same skeleton. In our preliminary experiments, however, the application of the same approach was

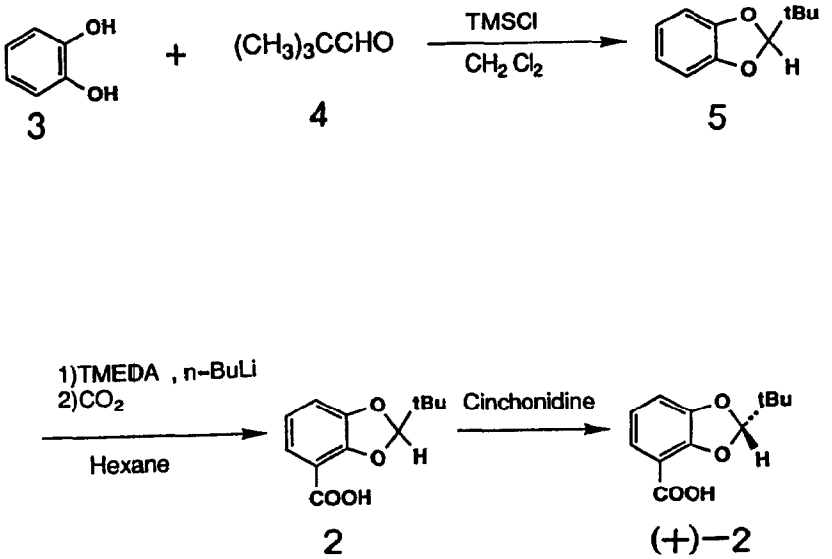


	R_1	R_2
(+)-1	CH_3	*tert*-Butyl
(+)-2	H	*tert*-Butyl

(Fig. 1)

unsuccessful when aldehyde for example, trimethylaldehyde was employed; the acetal formation with *p*-toluenesulfonic acid did not proceed, and the $KMnO_4$ oxidation of the acetal prepared in another way[9] resulted in a miserable yield of the desired acid (ca.1 %). In this communication, we wish to report an alternative approach towards a new chiral acid [(+)-2] with an acetal group at the C-2 position starting from catechol and trimethylacetaldehyde (scheme). It can be readily expected that this new acid (+)-2 would have a stronger separation ability in the enantiomeric analysis of chiral amines or alcohols than (+)-1 since the difference between the two alkyl groups at the C-2 position is expanded.

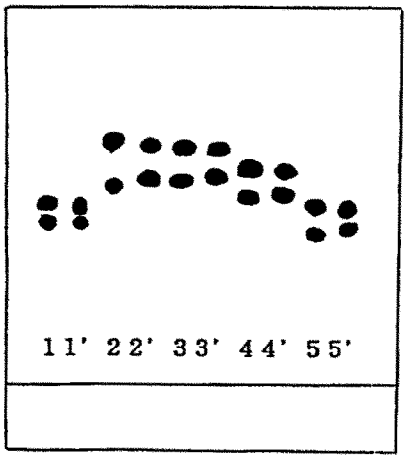
Trimethylsilyl chloride (TMSCl)[9] was used for the acetal formation of 3 with trimethylacetaldehyde 4, from which desired acetal 5 (mp. 38-39℃) was obtained in 91 % yield. Treatment of 5 with *n*-BuLi and N,N,N',N'-tetramethylethylenediamine (TMEDA) in *n*-hexane followed by solid carbon dioxide[10,11] gave a racemate 2 (mp.131-135 ℃) in 54% yield.



Scheme

The optical resolution of 2 was carried out in the same way as that of 1 with (-)-cinchonidine.[6] Repeated recrystalizations of the cinchonidine salt from boiling acetone gave optically pure (+)-2. mp. 133 ℃. $[\alpha]_D^{22}$ +52.6° (c, 0.5, MeOH). Circular dichroism (MeOH): 318 nm ($[\theta]$max = +1500). ^{1}H-NMR (ppm, $CDCl_3$): δ 1.06 (9H, s, *tert*-Bu), 5.96 (1H, s, H-2), 6.83, (1H, dd, J = 8 Hz and 8 Hz, H-6), 6.95 (1H, dd, J = 8 Hz and 1 Hz, H-7), 7.42 (1H, dd, J = 8 HZ and 1Hz, H-5). *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.84; H, 6.36. Found C, 64.74; H, 6.30.

The new carboxylic acid (+)-2 is a stable white crystalline solid with a fluorescence [Ex (max) 315 nm, Em (max) 360 nm]. Its absolute configuration is assumed to be (*S*) from the positive sign of CD and $[\alpha]_D$ compared with the (*S*)-configuration of (+)-1.[6b] In order to test the utility of (+)-2 as a chiral derivatizing agent, some D,L-amino acid methyl esters were derivatized with (+)-TBB carboxylic acid[6a], and the TLC separation was compared with that of the derivatives by (+)-1. Consequently, (+)-2 showed a constantly higher separation of the D and L-isomers of amino acids than (+)-1. This result is in accordance with the expectation as described above.



No 1 - 5 : (+)-TBB derivatives
1' - 5' : (+)-TBMB derivatives

1,1' : D,L-alanine
2,2' : D,L-leucine
3,3' : D,L-isoleucine
4,4' : D,L-valine
5,5' : D,L-phenylalanine

Fig. 2 TLC Separations of (+)-TBB and (+)-TBMB Derivatives of D,L-Amino Acid Methylesters. (Slica gel TLC, Kieselgel $60F_{254}$ (MERCK), Solvents: n-hexane-ethylacetate=4:1, Detection: fluorescence under UV lamp).

In conclusion, (+)-2 [(+)-TBB carboxylic acid] with an acetal moiety was first synthesized from catechol and trimethylacetaldehyde. Its potential as a chiral derivatizing agent was briefly compared with that of (+)-1 [(+)-TBMB carboxylic acid], and superior separations of D,L-isomers of amino acids resulted. This study also suggested that a series of chiral acids with the same skeleton can be prepared in the same manner. The study along this line will be continued by our group and reported in due course.

Acknowledgement: The authors are grateful to the Japanese Ministry of Education, Science and Culture and Research Development Corporation of Japan for the grants-in-aid to promote this study.

References:

1) J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, 1969, 21, 2543.
2) N. Nimura, A. Toyama and T. Kinoshita, *J. Chromatography*, 1984, 316, 547.
3) R. E. Doolittle and R. R. Heath, *J. Org. Chem.*, 1984, 49, 5041.
4) S. Erinarsson, B. Josefsson, P. Moller and D. Sanchez, *Anal. Chem.*, 1987, 59, 1191.
5) a) J. Goto, N. Goto, M. Itoh, A. Hongo, S. Nakamura and T. Namubara, *Anal. Science*, 1990, 6, 261.
   b) S. Miyano, S. Okada, H. Hotta, M. Takeda, C. Kabuto and H. Hashimoto, *Bull. Chem. Soc. Jpn.*, 1989, 62, 1528.
6) a) Y. Nishida, H. Ohrui and H. Meguro, *Tetrahedron Lett.*, 1989, 30, 5277.
   b) Y. Nishida, H. Ohrui, H. Meguro and C. Kabuto, *Anal Science*, 1991, 7, 349.
   c) Y. Nishida, *Kagaku & Seibutsu*, 1991, 29,647.
7) Y. Nishida, M. Kumagai, A. Kamiyama, H. Ohrui and H. Meguro, *Carbohydr. Res.*, 1991, 218, 63.
8) N. Harada and K. Nakanishi, '*Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*', University Science Books, California, USA, 1983.
9) T. H. Chan, M. A. Brook and T. Chaly, *Synthesis*, 1983, 203.
10) E. J. Corey and S. Bhattacharrya, *Tetrahedron Lett.*, 1977, 3919.
11) E. J. Corey and S. D. Hurt, *Tetrahedron Lett.*, 1977, 3923.