Agric. Chem. Biotechnol. **43**(2), 101-103(2000)

Synthesis and Optical Resolution of (±)-10,11-Dihydroxy-5*H*-dibenzo[a,d]cyclohepten-5-one

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Recevied January 24, 2000

The synthesis and resolution of (±)-10,11-dihydroxydibenzosuberenone 3, a potential pharmaceutical compound, is described. It was synthesized from the 5*H*-dibenzo[a,d]cycloheptene-5-one (dibenzosuberenone) 1, and converted to diastereomeric isomers using (*R*)-(+)-α-methylbenzylamine. Optical resolution of (±)-10,11-dihydroxydibenzosuberenone 3 was possible by fractional recrystallization of the diastereomer formed in ethanol. The optical resolution of 10,11-dihydroxydibenzosuberenone through formation of its phosphoamidates 5 using the (*R*)-(+)-α-methylbenzylamine was achieved. These compounds provided the optical rotation of [α] = −64.3 for (−)-10,11-dihydroxydibenzosuberenone and [α] = +61.3 for (+)-10,11-dihydroxydibenzosuberenone. The (−)- and (+)-enantiomers were prepared in five steps from dibenzosuberenone with overall yields of 11.66% and 9.38%, respectively.

Key words : *dibenzosuberenone, dihydroxydibenzosuberenone, optical resolution, recrystallization.*

An overwhelming majority of naturally occurring medicinal agents are chiral molecules; moreover, they exist in nature (and are marketed) mostly as a single enantiomer. In contrast, there has been an increasing demand in the field of organic synthesis to develop a new method to prepare optically active compounds.

Stereoselective disposition of enantiomers can result in different pharmacological profile owing to different rate of absorption or stereoselective presystemic metabolism, distribution or clearance. This can lead to the enantioselective or enantiospecific formation of metabolites exhibiting undesirable, possibly toxic, and side-effects. Therefore, with the recent achievements in the industrial-scale preparation of pure enantiomers using synthetic or biotechnological methods, the drug registration authorities already prefer enantiometrically pure new drugs to the corresponding racemates and this tendency will certainly increase in the near future.

A number of heterocyclic compounds involving dibenzo [a,d]cycloalkenes have been of interest due to their useful medicinal activity.[1,2] In addition, some structural analogues of 5*H*-dibenzo[a,d]cycloheptene are common substructures of variety of pharmacologically and clinically active compounds such as protriptyline[3] and butaclamol.[4]

Resolution of racemate is one of the broad methods, either diastereomeric or enzymatic, to obtain enantiomers. In diastereomeric resolution a pair of enantiomers (racemates) react with an optically pure resolving agent to a physicochemically non-identical covalent derivatives or salts, which can be easily separated by chromatography or recrystallization. The obtained diastereomers are decomposed to the separated enantiomers. Consequently, in this paper, new diol derivative **3** of 5*H*-dibenzo [a,d]cyclohepten-5-one **1** was synthesized and resolved by converting them into diastereomeric compounds with the resolving agent of (*R*)-(+)-α-methylbenzylamine, followed by fractional recrystallization.

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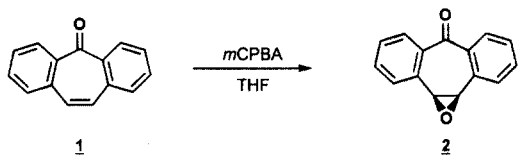
Materials and Methods

Materials. 5*H*-Dibenzo[a,d]cyclohepten-5-one (dibenzosuberenone), *m*-chloroperoxybenzoic acid (*m*CPBA), (*R*)-(+)-α-methylbenzylamine, phosphoroxytrichloride, and triethylamine were purchased from Aldrich (Milwaukee, WI, USA). Tetrahydrofuran (THF) and diethylether were distilled from potassium/benzophenone, and acetone was dried with anhydrous K_2CO_3 and then distilled. Dichloromethane was pre-dried with $CaCl_2$, and distilled from P_2O_5. These solvents were stored in round flasks with Linde type 4Å molecular sieves under an atmosphere of dry-Ar. All other solvents and reagents used were of analytical or reagent grade.

Specific rotations were measured on an AA-10 digital polarimeter (Optical Activity; Huntingdon, UK) at 25°C. IR spectra were recorded on a Spectrum BX (Perkin-Elmer; Avondale, CA, USA). ^{1}H-NMR and mass spectra were taken on a Gemini 300 (Varian; Hansen, CA, USA) with a tetramethylsilane as an internal standard and an HP 5989B Mass Spectrometer directly interfaced to a HP 5890 gas

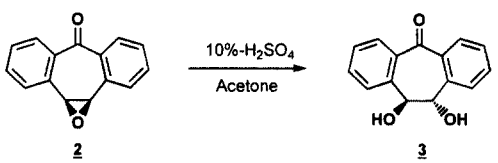
chromatograph (Hewlett-Packard; Foster, CA, USA) by electron impact (EI) at 70 eV.

Preparation of 10,11-epoxydibenzosuberenone 2. A mixture of dibenzosuberenone **1** (4.125 g, 20 mmole), *m*CPBA (30 g), and dried THF (100 mL) was stirred under Ar-gas for 3 h at 0°C and then at room temperature for 1 h. The reaction mixture was dilute with diethylether (300 mL), washed with 1%-ice cold aqueous NaOH (3×100 mL) and distilled water, and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a pale yellow liquid (3.69 g, 89.19% yield, scheme 1).



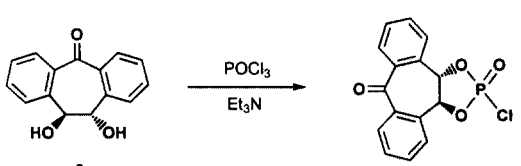
Scheme 1.

Preparation of 10,11-dihydroxydibenzosuberenone 3. A solution of 10%-H_2SO_4 (10 mL) was dropwised to a solution of 10,11-epoxydibenzosuberenone **2** (2.22 g, 10 mmole) in acetone (50 mL). The mixture was stirred at room temperature for 24 h. It was then diluted with ice cold water (100 mL), washed with 2%-$NaHCO_3$ and saturated brine, and dried over anhydrous-$MgSO_4$. Evaporation of the solvent gave a pale yellow solid (2.06 g, 85.83% yield, scheme 2).



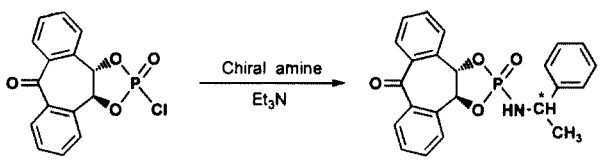
Scheme 2.

Preparation of 10,11-phosphorylchlorodibenzosuberenone 4. To a solution of 10,11-dihydroxydibenzosuberenone **3** (14.42 g, 60 mmole) in dichloromethane (200 mL), under Ar-gas was added phosphoroxytrichloride (4.5 mL), followed by the slow addition of triethylamine (11.5 mL) with stirring. After 1 h of additional stirring, the reaction mixture was washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a yellow crystalline solid (17.08 g, 88.96% yield, scheme 3).



Scheme 3.

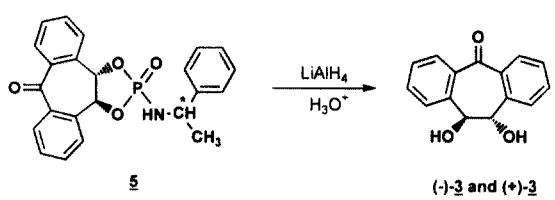
Preparation of 10,11-phosphorylaminodibenzosuberenone 5. A mixture of (*R*)-(+)-α-methylbenzylamine (7.09 mL, 55 mmole) and triethylamine (7 mL) in dichloromethane (300 mL) was dropwised into the stirred crude 10,11-phosphorychlorodibenzosuberenone **4** (15 g, 47 mmole) cooled in an ice-salt bath. After the addition (0.5 h), the mixture was stirred at room temperature for 36 h. The reaction mixture was washed with 4%-HCl and then with saturated brine and was dried over anhydrous $MgSO_4$. After the removal of solvent under reduced pressure, a diastereomer mixture of 10,11-phosphorylaminodibenzosuberenone **5** was obtained (12.06 g, 63.04% yield, scheme 4).



Scheme 4.

Separation of diastereomer of phosphorylaminodibenzosuberenone 5. A diastereomer of 10,11-phosphorylaminodibenzosuberenone (8.13 g, 20 mmole) of was dissolved in absolute ethanol (45 mL) under reflux. After 48 h at room temperature, the solution was concentrated by N_2 gas. Each evaporation step was adjusted to 5 mL for salting out of the compound. After fractional recrystallization, it afforded crystalline (+)-10,11-phosphorylaminodibenzosuberenone (+)-**5** ([α] = +53.4, c = 0.5, CH_2Cl_2; 1.26 g, 30.99% yield) and (−)-10,11-phosphorylaminodibenzosuberenone (−)-**5** ([α] = 51.8, c = 0.5, CH_2Cl_2; 1.07 g, 26.32% yield) in order.

Reduction of phosphorylaminodibenzosuberenone 5. Via the literature procedure,[5] colorless crystallines of (−)-10,11-dihydroxydibenzosuberenone (−)-**3** ([α] = −64.3, c = 0.1, THF) and (+)-10,11-dihydroxydibenzosuberenone(+)-**3** ([α] = +61.3, c = 0.1, THF) resulted in 87.63 and 83.01% yield, respectively.



Scheme 5.

Results and Discussion

Generally, optically active diols α-binaphthol (1,1-bi-2-naphthol; BINOL), for an example, are widely used in enantioselective organic reactions,[5-7] and therefore various methods for the resolution of the racemic diol have been developed. Recently for the resolution of 1,1-bi-2-naphthol, L-amino acids[8] and optically active phenethylamine[7] were

employed as a good resolving agents.

The reaction of (±)-10-phosphorylchlorodibenzosuberenone **4** with (*R*)-(+)-α-methylbenzylamine in ethanol resulted in two diastereomers, i.e. (+)- and (−)-salts of 10-phosphorylaminodibenzosuberenone **5**, which could be reduced to optically active 10,11-dihydroxy-5*H*-dibenzo [a,d]cyclohepten-5-one **3** as corresponding enantiomer with $LiAlH_4$ in THF. The spectral data of ^{1}H-NMR, FT-IR, and GC-MS are as follows: the chemical shift was recorded in ppm, and the reference was tetramethylsilane (TMS). ^{1}H-NMR (300 MHz, DMSO) δ; 4.5 (s, -OH, 1H), 7.3 (s, -CH, 1 H), 7.4-7.7 (m, $-C_6H_4$, 4H): FT-IR (CCl_4) cm^{-1}: 690-900 (= C-H), 1475-1600 (C = C), 1700 (C = O), 3200-3500 (OH): EI-MS (70eV), *m/z* (rel. int.): 240 (M^+, 3.2%), 222 (M-H_2O, 51.8%), 194 (222-$C_2H_4^+$, 92.6%), 165 (194-CHO^+, 100%).

In a racemic diol-derivative of dibenzosuberenone, the target molecule was prepared in two steps with an overall yield of 76.55%. Optical resolution of the present compound was achieved in three steps from racemic diol with overall yields of 15.23% and 12.25% as (−)- and (+)-enantiomers, respectively. According to the present preparation, the racemic diol can easily be resolved into each enantiomer. Consequently, further development of the present type organic synthesis will provide enantiomerically pure compounds.

References

1. Evans, B. E., Anderson, P. S., Christy, M. E., Colton, C. D., Remy, C. D., Rittle, K. E. and Engelhardt, E. L. (1979) Transannular reactions of dibenzo[a,d]cycloalkenes. 2. Synthesis of bridgehead substituted dibenzo[a,d] cycloalkenimines by a regiospecific transannular amine to olefin addition. *J. Org. Chem.* **44**, 3127-3135.
2. Leeson, P. D., Carling, R. W., James, K. and Baker, R. (1990) Transannular reactions of 5-azido- and 5-nitronodibenzo[a,d]cyclooctatrienes and dibenzo[a,d] cycloheptatrienes. Synthesis of Pavine and Homoisopavine analogues. *J. Org. Chem.* **55**, 2103-2108.
3. Olson, G. L., Cheung, H. C., Morgan, K. D., Blount, J. F., Todaro, L. and Berger, L. (1981) A dopamine receptor model and its application in the design of a new class of rigid pyrrolo[2,3-g]isoquinoline antipsychotics. *J. Med. Chem.* **24**, 1026-1034.
4. Lindner, H. J. (1981) Atomisierungsenergien gespannter konjugierter Kohlenwasserstoffe III. Konformationen konjugierter siebengliedriger Carbocyclen. *Tetrahedron* **37**, 535-543.
5. Kyba, E. P., Gokel, G. W., Jong, F., Koga, K., Sousa, L. R., Siegel, M. G., Kaplan, L., Sogah, G. D. Y. and Cram, D. J. (1977) Host-guest complexation. 7. The binaphthyl structural unit in host compounds. *J. Org. Chem.* **42**, 4173-4184.
6. Toda, F. and Tanaka, K. (1988) Efficient optical resolution of 2,2-dihydroxy-1,1-binaphthyl and related compounds by complex formation with novel chiral host compounds derived from tartaric acid. *J. Org. Chem.* **53**, 3607-3609.
7. Gong, B. Q., Chen, W. Y. and Hu, B. F. (1991) A new efficient method for the resolution of 2,2-dihydroxy-1,1-binaphthyl. *J. Org. Chem.* **56**, 423-425.
8. Periasami, M., Venkatraman. L. and Thomas, K. R. J. (1997) New methods of resolution and enrichment of enantiomeric excesses of 1,1-bi-2-naphthol. *J. Org. Chem.* **62**, 4302-4306.