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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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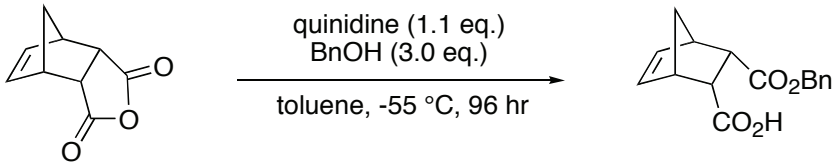
ASYMMETRIC ALCOHOLYSIS OF MESO-ANHYDRIDES MEDIATED BY ALKALOIDS

(Bicyclo[2.2.1]hept-5-ene-2-endo-carboxylic acid, 3-endo-benzyloxycarbonyl, (2*R*,3*S*)-)



Submitted by Carsten Bolm,[1] Iuliana Atodiresei and Ingo Schiffers.
Checked by Motomu Kanai and Masakatsu Shibasaki.

1. Procedure

A flame-dried 250-mL single-necked, round-bottomed flask equipped with a magnetic stirring bar and charged with quinidine (7.14 g, 22 mmol) (Note 1) and *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (3.28 g, 20 mmol) (Note 2) is placed under vacuum for 2 h (Note 3). The evacuated flask is flushed with argon, charged with 100 mL of dry toluene (Note 4), equipped with a rubber septum and the mixture is cooled to -55 °C (Note 5). Benzyl alcohol (6.2 mL, 6.49 g, 60 mmol) (Note 6) is added dropwise via syringe (over a period of 10 min) to the cooled suspension (Note 7), and the reaction mixture is stirred at the indicated temperature for 96 h (Note 8), during which the solid material gradually dissolves. The resulting clear solution is concentrated *in vacuo* to dryness, and the resulting residue is dissolved in diethyl ether (125 mL). The solution is washed with 2 N HCl (3 × 30 mL), and the aqueous layer is back-extracted with ether (5 × 50 mL). The combined organic layers are extracted with a saturated solution of sodium bicarbonate (5 × 75 mL), and the resulting aqueous phase is washed with diethyl ether (1 × 100 mL) in order to remove the traces of benzyl alcohol. The aqueous phase is acidified with 8 N HCl, extracted with CH_2Cl_2 (5 × 100 mL), and the combined organic layers are dried ($MgSO_4$), filtered and concentrated to provide 4.97-5.20 g (91-95%, 97-98% ee) of the benzyl hemiester as a white solid (Note 9). The enantiomeric excess of the half ester was analyzed by chiral HPLC analysis (Note 10). Alternatively, the enantiomeric excess of the benzyl ester[2] could be determined by GC analysis of the corresponding lactone,[3] which was obtained by selective

reduction of the ester group with lithium triethylborohydride ($LiBEt_3H$) followed by acid-catalyzed lactonization (Note 11).[4]

Use of quinine in the ring opening of *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride provides 5.13 g (94%) of the corresponding enantiomeric benzyl hemiester as a white solid (Note 16).

2. Notes

1. Anhydrous quinidine (95%) and quinine (99%) were purchased from Acros Organics and used as supplied.

2. *Endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (97%) was purchased from Fluka and used as received.

3. High vacuum is used in order to remove traces of moisture.

4. Toluene (Merck, >99%), distilled from sodium benzophenone ketyl radical under argon, was stored over 4 Å molecular sieves.

5. An RL 6 CP type cooling machine was used in order to maintained the low temperature.

6. Anhydrous benzyl alcohol (99.8%) was purchased from Sigma-Aldrich and used as supplied.

7. The mixture is stirred for at least 1 h at the indicated temperature before the benzyl alcohol addition.

8. The reaction has been studied extensively on a 1-mmol scale, and the best asymmetric induction was achieved when the reactions were performed at low temperature. Slightly lower enantioselectivities have been observed when the desymmetrizations were carried out at room temperature.

9. The product has the following characteristics: mp 120 °C (racemate), 88-90 °C (enantiomer); $[\alpha]_D^{rt}$ = +6.6 (c = 1.90, $CHCl_3$); ee = 97-98% (GC-analysis of the lactone: Lipodex E, t_1 = 89.3, t_2 = 89.8 major); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (d, J = 8.6 Hz, 1H), 1.48 (dt, J = 8.6, 1.8 Hz, 1H), 3.18 (br s, 1H), 3.30 (br s, 1H), 3.31-3.35 (m, 2H), 4.91 (d, J = 12.6 Hz, 1H), 5.09 (d, J = 12.6 Hz, 1H), 6.22 (dd, J = 3.0, 5.7 Hz, 1H), 6.30 (dd, J = 3.0, 5.7 Hz, 1H), 7.27-7.36 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 46.1, 46.5, 48.1, 48.2, 48.7, 66.3, 128.0, 128.2, 128.4, 134.3, 135.5, 135.8, 172.2, 178.7; IR (KBr) 3065, 3032, 2979, 1740, 1707, 1172 cm^{-1}; EI-MS m/z = 272 (M^+, 2), 254 (3), 226 (3), 181 (58), 163 (3), 137 (5), 119 (2), 91 (100), 66 (20). Anal. Calcd for $C_{16}H_{16}O_4$ (272.30): C 70.57; H 5.92. Found: C 70.55; H 6.01.

10. Conditions: Daicel CHIRALPAK AS-H, eluent = ^{i}PrOH/hexane = 1/1, flow = 0.5 mL/min, detection = 254 nm, retention time = 10 mi (minor isomer using quinidine) and 12 min (major isomer using quinidine).

11. General procedure for the lactone formation. A 25-mL flame-dried Schlenk-flask equipped with a magnetic stirring bar and rubber septum is purged with argon and charged with (2*R*,3*S*)-3-*endo*-benzyloxycarbonyl bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (80 mg, 0.29 mmol) in THF (2 mL) (Note 12). The reaction mixture is cooled to 0 °C with an ice-bath and 6 eq. of $LiBEt_3H$ (2 mL, 1 M solution in THF) (Note 13) are slowly added. After stirring for 1 h at room temperature 2 N HCl (5 mL) is slowly added and the mixture is stirred for additional 2 h. The aqueous phase is extracted with ethyl acetate (3 × 5 mL), and the combined organic phases are dried over $MgSO_4$ and filtered. Evaporation of the solvent yields the corresponding lactone, which is analyzed by GC (Note 14).

In order to recover the alkaloid, the acidic aqueous phase, obtained after the first extraction, is neutralized with Na_2CO_3 and extracted with CH_2Cl_2 (5 × 100 mL). The combined organic phases are dried over $MgSO_4$ and filtered. Evaporation of the solvent yields the alkaloid almost quantitatively (6.93 g, 21.36 mmol, 97%) (Note 15).

12. THF was distilled from sodium benzophenone ketyl radical under argon.

13. $LiBEt_3H$ was purchased from Acros Organics and used as received.

14. Capillary gas chromatograms were obtained using the following column and temperature program: Lipodex E: 2,6-*O*-Dipentyl-3-*O*-butyryl-γ-CD. Column head pressure: 1.0 bar N_2; 100 °C (50 min), heating rate 3.0 °C/min up to 180 °C (60 min). Injector temperature 200 °C, detector temperature 250 °C.

15. The spectral properties of the recovered alkaloid were in accordance with the data published in the literature.[5]

16. The reaction was performed in a 0.1 M solution (with respect to the anhydride) to give (2*S*,3*R*)-3-*endo*-benzyloxycarbonyl-bicyclo [2.2.1] hept-5-ene-2-*endo*-carboxylic acid with 96% ee (GC-analysis of the lactone: Lipodex E, t_1 = 89.3, major, t_2 = 89.8); $[\alpha]^{rt}_D = -7.4$ (c = 1.00, $CHCl_3$).

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described above is an improved version of previously reported alkaloid-mediated asymmetric anhydride openings.[2,3,6,7] Structurally diverse anhydrides have been converted into their corresponding benzyl monoesters with very high enantiomeric excesses and excellent yields. (Table 1) Both enantiomers are available by using either quinidine or quinine as directing additive. An advantage of the present protocol using benzyl alcohol as the nucleophile is that the reactions can be performed using toluene as solvent, avoiding the use of the previously utilized carbon tetrachloride. A simple aqueous work-up permits the isolation of the products in analytically pure form. The synthetic usefulness of the method was demonstrated by the preparation of optically active β-amino acids[2] and unsymmetrical norbornane scaffolds as inducers for hydrogen bond interactions in peptides.[8] In these applications, the benzyl hemiesters were converted into the corresponding *N*-Cbz-protected β-amino acid benzyl esters by Curtius degradation, which proceeded with neither racemization nor epimerization. Subsequent cleavage of both protecting groups by simple hydrogenation yielded the corresponding free β-amino acids in excellent yields in a single step. Finally, the method is also highly selective for the preparation of the corresponding methyl hemiesters, which have been isolated with up to 99% yield and 99% ee (on a 1 mmol scale). The usefulness of such products for the synthesis of optically active β-amino acids, 1,2-diamines, and polymeric materials has also already been demonstrated.[9]

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2. Bolm, C.; Schiffers, I.; Atodiresei, I.; Hackenberger, C. P. R. *Tetrahedron: Asymmetry* **2003**, *14*, 3455.

3. (a) Bolm, C.; Gerlach, A.; Dinter, C. L. *Synlett* **1999**, 195. (b) Bolm, C.; Schiffers, I.; Dinter, C. L.; Gerlach, A. *J. Org. Chem.* **2000**, *65*, 6984.

4. Jaeschke, G.; Seebach, D. *J. Org. Chem.* **1998**, *63*, 1190.

5. Raheem, I. T.; Goodman, S. N.; Jacobsen, E. N. *J. Am. Chem. Soc.*, **2004**, *126*, 706.

6. (a) Hiratake, J.; Inagaki, M.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1053. (b) Hiratake, J.; Yamamoto, Y.; Oda, J. *J. Chem. Soc., Chem. Commun.* **1985**, 1717. (c) Aitken, R. A.; Gopal, J. *Tetrahedron: Asymmetry* **1990**, *1*, 517. (d) Aitken, R. A.; Gopal, J.; Hirst, J. A. *J. Chem Soc., Chem. Commun.* **1988**, 632.

7. For recent reviews, see: (a) Chen, Y.; McDaid, P.; Deng, L. *Chem. Rev.* **2003**, *103*, 2965. (b) Tian, S.-K.; Chen, Y.; Hang, J.; Tang, L.; McDaid, P.; Deng, L. *Acc. Chem. Res.* **2004**, *37*, 621; (c) Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem Rev.*, accepted for publication.

8. Hackenberger, C. P. R.; Schiffers, I.; Runsink, J.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 739.

9. (a) Bolm, C.; Schiffers, I.; Dinter, C. L.; Defrère, L.; Gerlach, A.; Raabe, G. *Synthesis* **2001**, 1719. (b) Bolm, C.; Dinter, C. L.; Schiffers, I.; Defrère, L. *Synlett* **2001**, 1875. (c) Bolm, C.; Schiffers, I.; Atodiresei, I.; Ozcubukcu, S.; Raabe, G. *New J. Chem.* **2003**, *27*, 14.

10. *cis*-1,2-Cyclobutanedicarboxylic anhydride was obtained by refluxing *cis*-cyclobutane-1,2-dicarboxylic acid (Fluka, >97%) in trifluoroacetic anhydride (Acros Organics, 99+%) for 16 h.

11. *cis*-1,2-Cyclopentanedicarboxylic anhydride was prepared in a 3-step synthesis according to a literature procedure. Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817.

12. *cis*-1,2-Cyclohexanedicarboxylic anhydride (99%) was purchased from Acros Organics and used as received.

13. *Exo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride was prepared according to a literature procedure. Canonne, P.; Belanger, D.; Lemay, G. *J. Org. Chem.* **1982**, *47*, 3953. It is also available from Sigma-Aldrich (95%).

14. *Exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride was prepared by Diels-Alder reaction of maleic anhydride and furan. It is also available from different commercial suppliers (Fluka, Sigma-Aldrich, Acros Organics, Lancaster Synthesis).

Appendix
Chemical Abstracts Nomenclature; (Registry Number)

Quinidine: Cinchonan-9-ol, 6'-methoxy-, (9S)-; (56-54-2)

endo-Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride: 4,7-Methanoisobenzofuran-1,3-dione, 3a,4,7,7a-tetrahydro-, (3aR,4S,7R,7aS)-rel-; (129-64-6)

Benzyl alcohol: Benzenemethanol; (100-51-6)

Lithium triethylborohydride: Borate(1-), triethylhydro-, lithium, (T-4)-; (22560-16-3)

Quinine: Cinchonan-9-ol, 6'-methoxy-, (8α,9R)-; (130-95-0)

Table 1. Quinidine-mediated ring opening of various meso-anhydrides with benzyl alcohol.[a]

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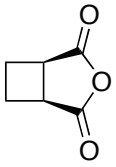
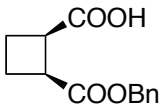
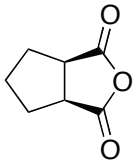
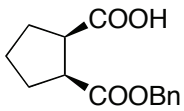
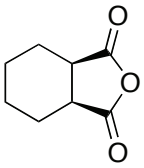
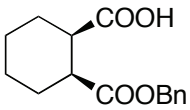
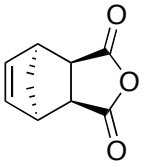
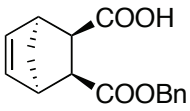
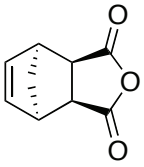
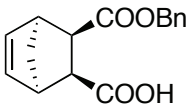
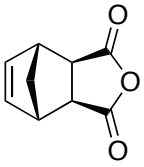
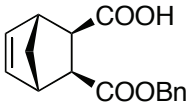
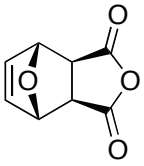
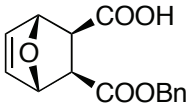
1			97	96
2			93	97
3			95	97
4			95	97
5[d]			94	96
6			97	96
7			89[e]	99

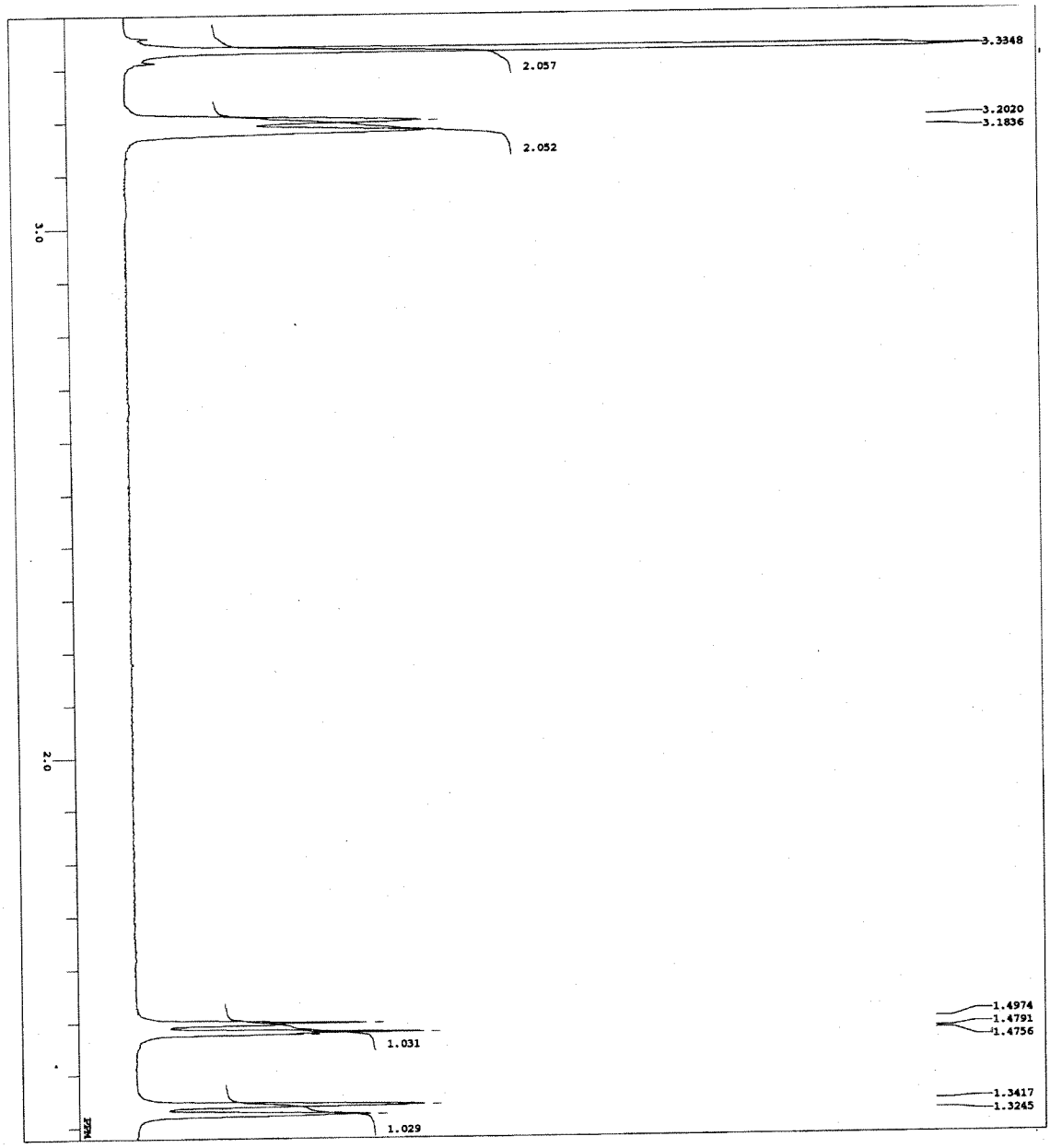
[a] All reactions were performed in toluene, at –55 °C for 96 hr using 1.1 eq. of quinidine and 3 eq. of benzyl alcohol in a 0.2 M solution related to anhydride. All products have been fully characterized.

[b] All meso-anhydrides were prepared by application of literature procedures or were commercially available. For specific procedures, see ref. 10-14.

[c] Determined by GC-analysis of the corresponding lactones using a chiral stationary phase. For retention times, see ref. 3b.

[d] Quinine was used as chiral mediator (0.1 M solution related to anhydride).

[e] After chromatographic purification.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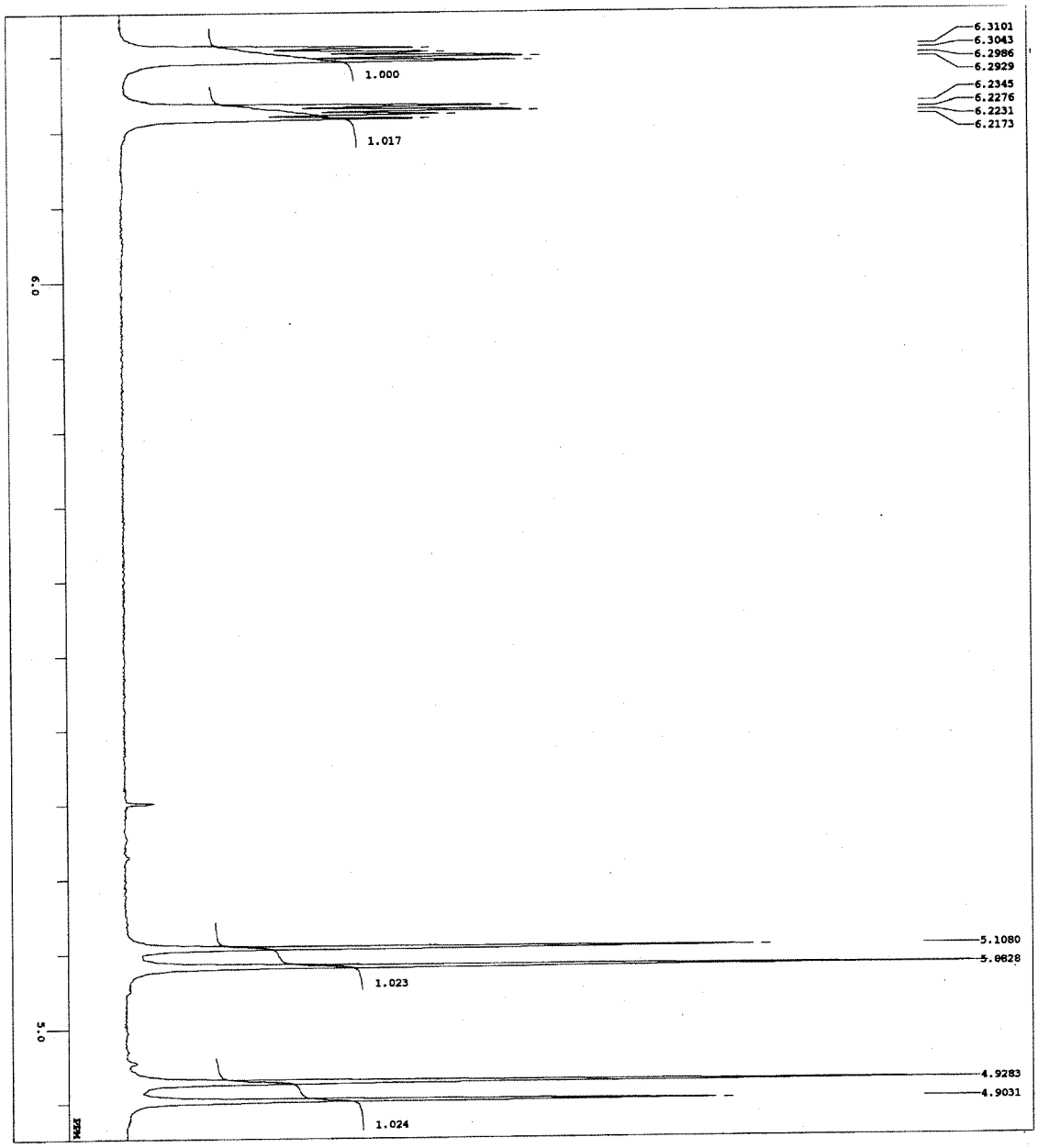
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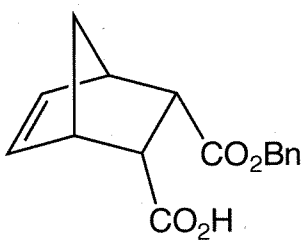
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