A Phosphine-Catalyzed [3+2] Cycloaddition Strategy Leading to the First Total Synthesis of (–)-Hinesol

*Yishu Du and Xiyan Lu**

State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry,

Chinese Academy of Sciences, 354 Fenglin Lu, Shanghai 200032, China

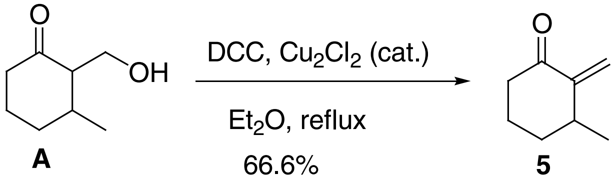
xylu@pub.sioc.ac.cn

Supporting Information

Table of Contents

General: For ^{13}C NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (77.00 ppm for ^{13}C NMR) as an internal reference.

Synthesis of compound 5



Compound **A** (a mixture of *cis* and *trans* isomers) was prepared by the reported method.[1]

2-Hydroxymethyl-3-methylcyclohexanone (A):

Oil. ^{1}H NMR (300 MHz, $CDCl_3$) 3.92-3.85 (m, 1H), 3.77-3.70 (m, 1H), 2.73-2.68 (m, 1H), 2.4-1.4 (m, 8H), 1.09 (d, *J* = 6.4 Hz, 3H).

Compound **5** was synthesized according to a procedure similar to that described by Alexandre.[2] To a solution of compound **A** (3.10 g, 21.8 mmol) and DCC (4.50 g, 21.8 mmol) in dry Et_2O (15 mL) was added Cu_2Cl_2 (80 mg) at room temperature. After 2.5 h of refluxing, the resulting suspension was cooled and filtered, concentrated under vacuum and the residue was purified by column chromatography on silica gel (eluent: petroleum ether (30-60 °C) / Et_2O = 1/20 ~ 1/10) to afford 1.80 g (±)-**5** in a 67% yield as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) 5.79 (br s, 1H), 5.13 (br s, 1H), 2.60-2.46 (m, 2H), 2.35 (m, 1H), 2.03-1.73 (m, 4H), 1.15 (d, *J* = 6.7 Hz, 3H).

Typical procedure for the triphenylphosphine-catalyzed cycloaddition of 5 with 2:

A solution of **5** (1.2 mmol), **2** (1.0 mmol) and PPh_3 (0.1 mmol) in dry toluene (10 mL) was stirred under reflux for 24h. The resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give 61 mg of a mixture of compounds **6-9**, in a 23% yield.

Typical procedure for the tributylphosphine-catalyzed cycloaddition of 5 with 2:

A solution of **5** (1.2 mmol), **2** (1.0 mmol) and PBu$_3$ (0.1 mmol) in dry toluene (10 mL) was stirred at room temperature for 5 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give 108 mg of a mixture of compounds **6**-**9**, in a 41% yield.

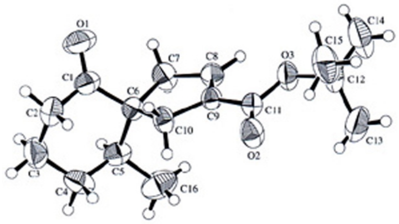
Typical procedure for the tributylphosphine-catalyzed cycloaddition of 5 with 3:

A solution of **5** (1.2 mmol), **3** (1.0 mmol) and PBu$_3$ (0.1 mmol) in dry toluene (10 mL) was stirred at room temperature for 23 h. The resulting mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel to give 166 mg of a mixture of compounds **6**-**9**, in a total 63% yield. Compound **6** was isolated by further column chromatography on silica gel using petroleum ether and ethyl acetate as the eluent.[3]

***tert*-Butyl (5*S**, 10*S**)-10-methyl-6-oxo-spiro[4.5]dec-2-ene-2-carboxylate ((5*S**, 10*S**)-6):**

White solid: mp 79-81 $^{\circ}$C (petroleum ether / ethyl acetate). IR (KBr) 2974, 2931, 1708, 1639, 1172 cm^{-1}. ^{1}H NMR (400 MHz, CDCl$_3$) 6.57-6.54 (m, 1H), 3.46 (dd, J = 19.2, 2.0 Hz, 1H), 2.76 (d, J = 17.1Hz, 1H), 2.52-2.42 (m, 3H), 2.19 (d, J = 19.2 Hz, 1H), 2.1-1.8 (m, 1H), 1.75-1.57 (m, 4H), 1.47 (s, 9H), 0.91 (d J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) 212.3, 164.0, 141.1, 134.4, 80.3, 59.4, 42.3, 38.8, 38.4, 35.8, 29.9, 28.1, 25.1, 15.8. MS (m/z) 208(M$^+$-C$_4$H$_8$), 193, 192(100), 191(M$^+$-O^{t}Bu), 190, 189, 57, 43, 41. Anal. Calcd for C$_{16}$H$_{24}$O$_3$: C, 72.69; H, 9.15. Found C, 72.99; H, 8.89. The stereo-structure of compound **6** was determined by X-ray analysis (Figure 1). Crystallographic data for (±)-**6**: C$_{16}$H$_{24}$O$_3$, F.W. = 264.36, orthorhombic, space group Pbca (#61), colorless, prismatic, 0.20 X 0.20 X 0.30 mm, a = 22.957(4) Å, b = 12.498(2) Å, c = 10.851(2) Å, V = 3113(1) Å^3, Z = 8, density (calcd) = 1.13g/cm^3; F(000) = 1152.00, T = 293 K, (MoK) = 0.76 cm^{-1}. The intensity data were collected on a Rigaku AFC7R diffractometer with MoK radiation (= 0.71069 Å, graphite monochromator), and a 12 kW rotating anode generator. The maximum 2 $_{\max}$ value was 55.0°; 2 range (13.7-21.4°); 3879 measured reflections. The 1489 reflections with I = 3.00 (I) were used in refinement; goodness of fit indicator, 1.85; R (Rw) = 0.050 (0.058); $S = 0.00$; $p_{\max}$, $p_{\min}$ = 0.19, -0.13 e^- / Å^3.

Figure 1. Crystal structure of compound **(5*S**, 10*S**)-6**



Hydrogenation of the spiro olefin (5*S, 10*S**)-6:**

Hydrogenation of the spiro olefin **6** (214 mg, 0.81 mmol) over Pd/C (5%, 40 mg) in 5 mL MeOH at room temperature and usual workup of the mixture afforded a minor product (**12**) (25 mg, 12%) and a major product (**13**) (188 mg, 87%). The ratio of the crude product was 13/87 (GC ratio **12/13**).

***tert*-Butyl (2*S**, 5*S**, 10*S**)-10-methyl-6-oxo-spiro[4.5]decane-2-carboxylate ((2*S**, 5*S**, 10*S**)-12):**

Oil. IR (neat) 2968, 2938, 1726, 1704, 1155 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) 2.74-2.63 (m, 1H), 2.56-2.46 (m, 1H), 2.38-2.22 (m, 2H), 2.16-2.08 (m, 1H), 2.05-1.4 (m, 18H), 0.92 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) 214.7, 175.4, 79.9, 61.6, 43.9, 42.2, 37.8, 35.2, 34.8, 29.7, 28.8, 28.0, 22.9, 15.9. MS (m/z) 193(M^+-O^tBu), 192, 165, 164, 67, 57 (100). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found C, 72.41; H, 9.85.

***tert*-Butyl (2*R**, 5*S**, 10*S**)-10-methyl-6-oxo-spiro[4.5]decane-2-carboxylate ((2*R**, 5*S**, 10*S**)-13):**

Oil. IR (neat) 2968, 2937, 1727, 1706, 1115 cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$) 2.67-2.59 (m, 1H), 2.48-2.29 (m, 3H), 2.08-1.4 (m, 19H), 0.94 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, CDCl$_3$) 213.6, 174.4, 80.1, 60.6, 45.3, 41.2, 38.4, 33.4, 32.7, 30.5, 29.3, 28.0, 24.3, 16.1. MS (m/z) 210(M^+- C_4H_8), 193(M^+- O^tBu), 147, 125, 57 (100), 55, 41. Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84. Found C, 72.49; H, 10.00.

Methyl (2*R**, 5*S**, 10*S**)-10-methyl-6-oxo-spiro[4.5]decane-2-carboxylate ((2*R**, 5*S**, 10*S**)-14):

tert-Butyl ester **13** (309 mg, 1.16 mmol) was directly converted to the methy ester by ester exchange in refluxing methanol (2.5 mL) in the presence of catalytic amount of concentrated H_2SO_4. After 24 hours and usual workup, **14** was obtained as a colorless oil. Yield: 93%. IR (neat) 2962, 1736, 1704 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 3.65 (s, 3H), 2.73 (m, 1H), 2.41 (t, *J* = 6.7 Hz, 2H), 2.32 (ddd, *J* = 12.9, 7.6, 3.2 Hz, 1H), 2.11 (dd, *J* = 13.5, 8.0 Hz, 1H), 1.98-1.64 (m, 7H), 1.60-1.42 (m, 2H), 0.92 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 213.6, 175.5, 60.6, 51.7, 44.0, 41.1, 38.2, 33.6, 33.0, 30.3, 29.1, 24.0, 16.0. MS (m/z) 224 (M^+), 147, 125 (100), 120, 109, 108, 107, 93, 67. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found C, 69.47; H, 9.22.

Methyl (2*R**, 5*S**, 10*S**)-10-methyl-6-methylene-spiro[4.5]decane-2-carboxylate (15)[4]:

CH_2I_2 (0.32 mL) was added at 25 °C to a stirring suspension of zinc (freshly activated, 0.48 g, 7.2 mmol) in THF (8 ml) under an argon atmosphere. After 0.5h, a solution of $TiCl_4$ (1 M solution in CH_2Cl_2, 0.74 mL) was added at 0 °C and the resulting brown mixture was stirred at room temperature for 30 min. Ester **14** (80 mg, 0.36 mmol) in THF (2 mL) was added dropwise to the above mixture at room temperature. After 15 min, the resulting mixture was then diluted with Et_2O and the reaction was quenched by saturated NH_4Cl solution. Usual workup of the mixture afforded **15** as colorless oil in an 82% yield. ^1H NMR was identical with which that described by Liang.[4] IR (neat) 2934, 1738, 1638, 1201, 1170 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) 4.74 (s, 1H), 4.62 (s, 1H), 3.66 (s, 3H), 2.79 (m, 1H), 2.2-1.2 (m, 13H), 0.85 (d, *J* = 7.1 Hz, 3H). MS (m/z) 222 (M^+), 162, 107 (100), 106, 95, 93, 91, 79, 67.

(2*R**, 5*S**, 10*S**)-Hinesol ((±)-1):[4,5]

Compound **15** (28 mg, 0.13 mmol) was added to a mixture of TsOH (4 mg) in benzene (4 mL) at room temperature. After 10 h of refluxing, the resulting mixture was chromatographed on silica gel, affording *endo*-olefin (26 mg) as colorless oil in a 93% yield.

The *endo*-olefin (18 mg) in Et_2O (2 mL) was added dropwise to an ice-cold solution of methylmagnesium iodide (16 equiv.) in dry ether (16 mL). The mixture was stirred for 30 min at 0 °C and then at room temperature for 3h. A few drops of water were added to the reaction mixture to quench the reaction. After the mixture was stirred for 15 min, the resulting mixture was dried ($MgSO_4$) and concentrated under vacuum. The residue was chromatographed on silica gel (eluent: n-hexane/ethyl acetate 10/1) to afford 17 mg **1** as a colorless oil in a 94% yield. The IR (lit.[5a]), ^{1}H NMR (lit.[4]) ^{13}C NMR (lit.[5b]) data were identical with those of the literatures. IR (CCl_4) 3610, 3401, 3026, 2964, 2925, 2878, 1660, 1471, 1458, 1378, 1365, 1222, 1194, 1170, 1134, 1103, 1080, 937, 917, 799 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) 5.33 (br s, 1H), 2.0-1.9 (m, 3H), 1.8-1.26 (m, 13H), 1.21 (s, 6H), 0.93 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) 140.03, 121.63, 71.95, 51.35, 48.67, 36.65, 35.61, 33.21, 28.38, 27.95, 27.91, 27.64, 24.17, 19.86, 16.16. MS (m/z) 222 (M^+), 161 (100), 119, 107, 91, 55, 43, 41. EI-HRMS calcd for $C_{15}H_{26}O$ 222.1984, found 222.1671.

References and Notes

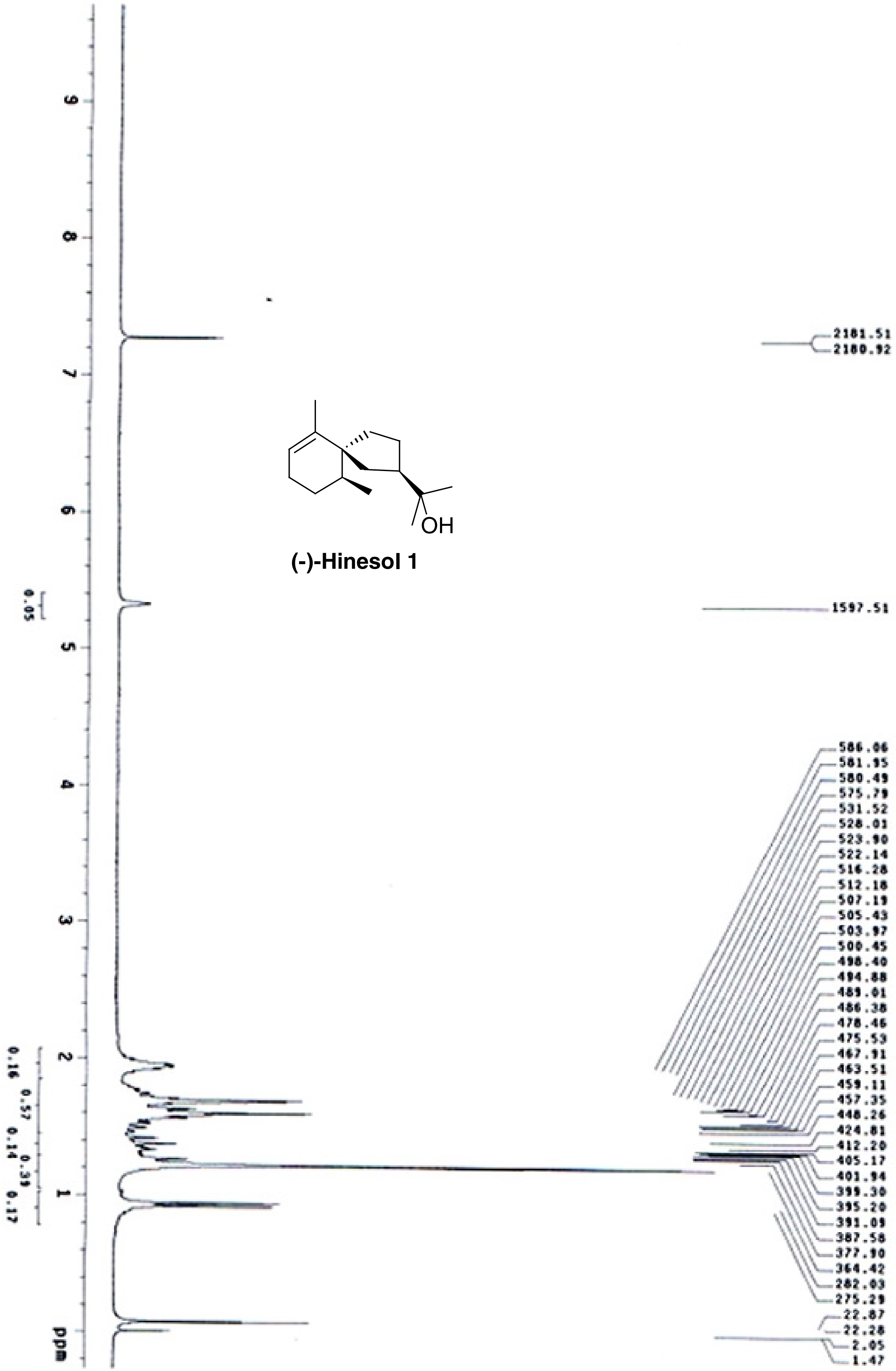
(1) Stork, G.; d'Angelo, J. *J. Am. Chem. Soc.* **1974**, *96*, 7114.

(2) Alexandre, C.; Rouessac, F. *Bull. Soc. Chem. Fr.* **1971**, 1837.

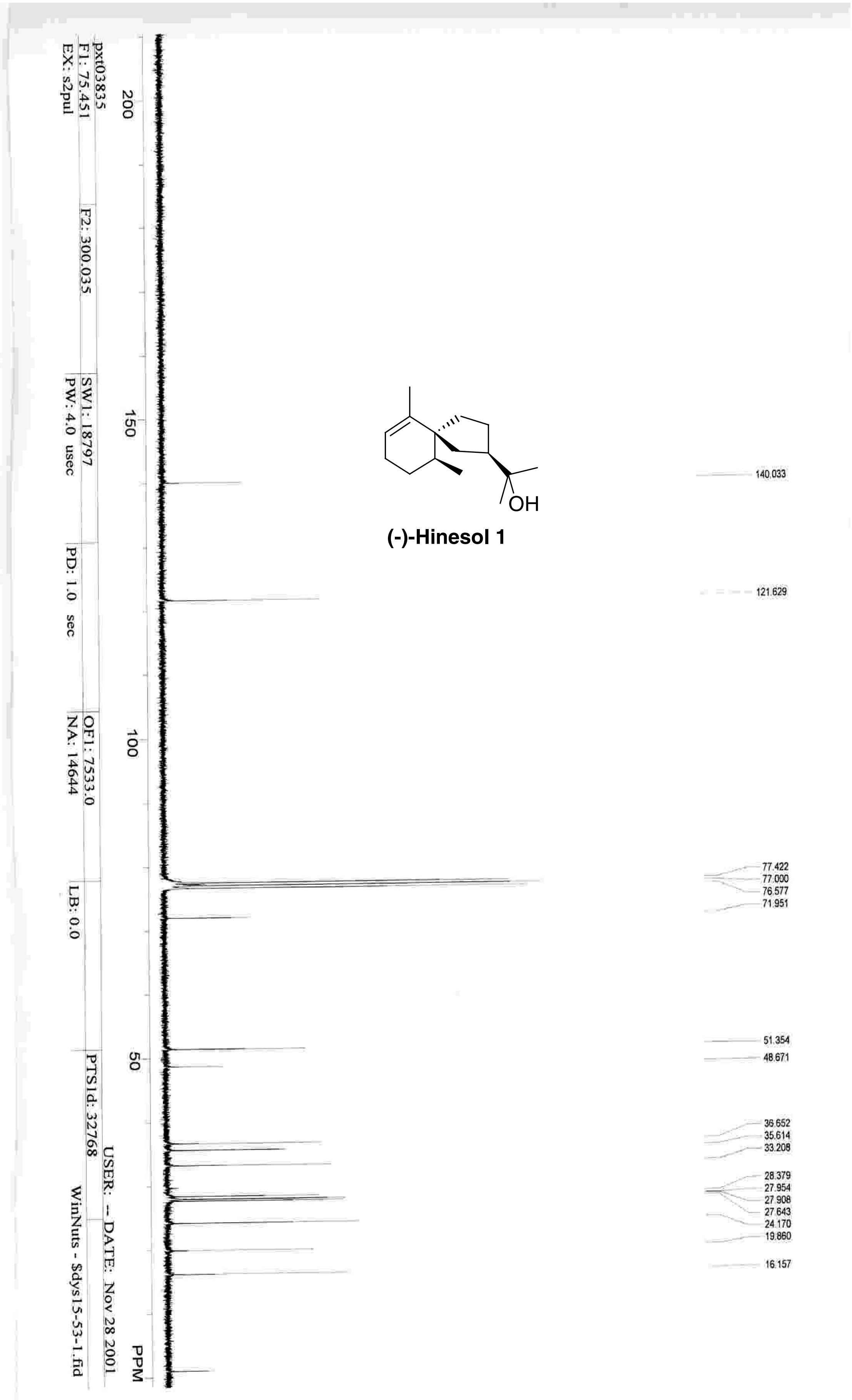
(3) Only the major [3+2] cycloadduct **6** was isolated and identified.

(4) Xie, P.; Chen, S. F.; Liang, X. T. *Chin. Chem. Lett.* **1998**, *9*, 353.

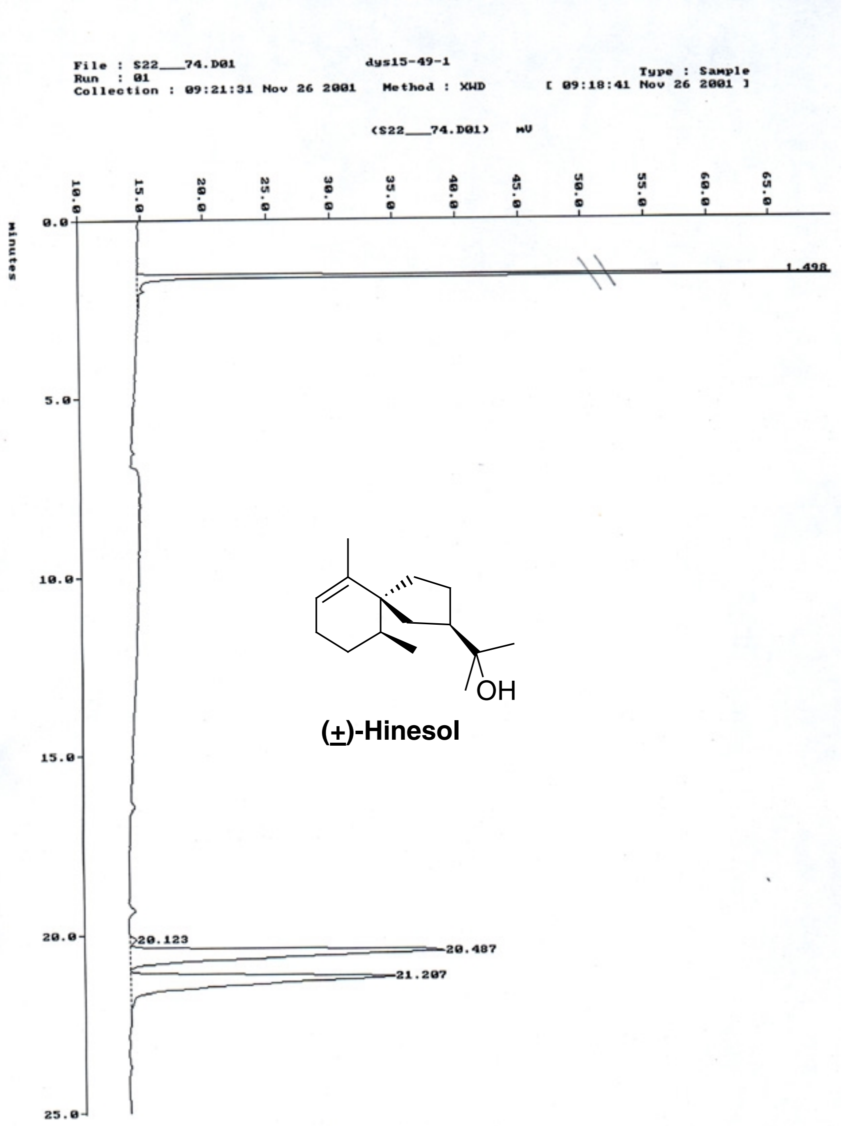
(5) (a) Ibuka, T.; Hayashi, K.; Minakata, H.; Ito, Y.; Inubushi, Y. *Can. J. Chem.* **1979**, *57*, 1579. (b) Nyström, J.-E.; Helquist, P. *J. Org. Chem.* **1989**, *54*, 4695.

9
8
7
6
5
4
3
2
1
ppm
0.05
0.16
0.57
0.14
0.39
0.17
2181.51
2180.92
1597.51
586.06
581.95
580.49
575.79
531.52
528.01
523.90
522.14
516.28
512.18
507.19
505.43
503.97
500.45
498.40
494.88
489.01
486.38
478.46
475.53
467.91
463.51
459.11
457.35
448.26
424.81
412.20
405.17
401.94
399.30
395.20
391.09
387.58
377.90
364.42
282.03
275.29
22.87
22.28
2.05
1.47
OH

(-)-Hinesol 1


pxt03835
F1: 75.451
EX: s2pul
F2: 300.035
SW1: 18797
PW: 4.0 usec
PD: 1.0 sec
OF1: 7533.0
NA: 14644
LB: 0.0
PTS1d: 32768
USER: -- DATE: Nov 28 2001
WinNuts - $dys15-53-1.fid
200
150
100
50
PPM
OH
140.033
121.629
77.422
77.000
76.577
71.951
51.354
48.671
36.652
35.614
33.208
28.379
27.954
27.908
27.643
24.170
19.860
16.157

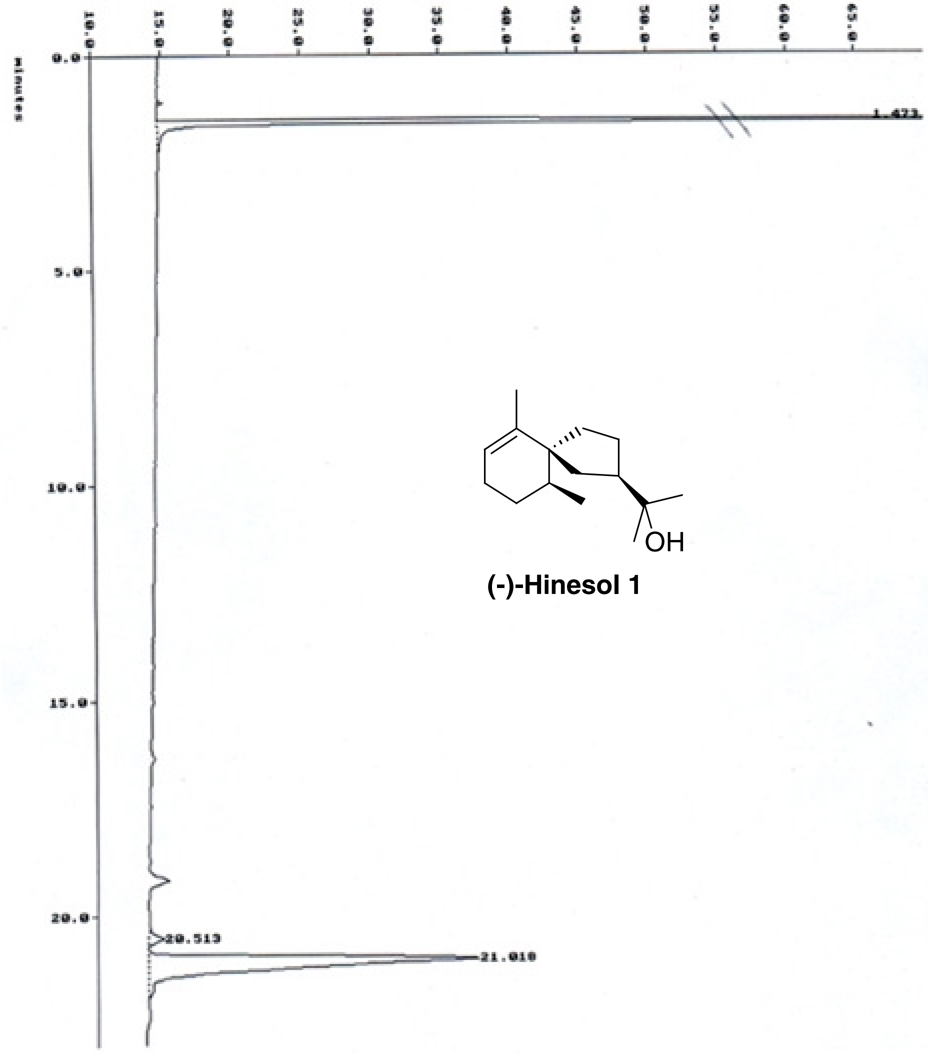
(-)-Hinesol 1



(±)-Hinesol

```
File : S22___74.D01                dys15-49-1
Run  : 01                                                  Type : Sampl
Path : C:\$T$                                            Inst : 1022 LC Plu
Collection : 09:21:31 Nov 26 2001   Method : XWD     [ 09:18:41 Nov 26 2001 ]
Integration: 09:21:31 Nov 26 2001   Method : XWD     [ 09:18:41 Nov 26 2001 ]
Report     : 16:32:39 Nov 30 2001   Method : XWD     [ 15:48:23 Nov 30 2001 ]

                       PERCENT ( AREA ) \ MANUALLY ALTERED

Pk #    RT        Area        Height  BC    Area Percent  Height Percent

  1   1.498          0        0.0317           -0.0000          0.0692
  2  20.123      54885        0.5165 T          0.7582          1.1273
  3  20.487    3605502       24.6685 T         49.8049         53.8427
  4  21.207    3578870       20.5992           49.4370         44.9608

   4 Peaks > Area Reject       7239257 Total Area
   4 Peaks > Height Reject      45.816 Total Height
```

```
File : S22___75.D01               dys15-53-1
Run  : 01                                                       Type : Sample
Collection : 10:07:27 Nov 26 2001   Method : XWD        [ 09:18:41 Nov 26 2001 ]

                                   (S22___75.D01)    mV
```



(-)-Hinesol 1

```
File : S22___75.D01                dys15-53-1
Run  : 01                                                    Type : Sampl
Path : C:\$T$                                                Inst : 1022 LC Plu
Collection : 10:07:27 Nov 26 2001   Method : XWD      [ 09:18:41 Nov 26 2001 ]
Integration: 10:07:27 Nov 26 2001   Method : XWD      [ 09:18:41 Nov 26 2001 ]
Report     : 16:52:10 Nov 30 2001   Method : XWD      [ 15:48:23 Nov 30 2001 ]

                         PERCENT ( AREA ) \ MANUALLY ALTERED

Pk #     RT        Area         Height  BC    Area Percent  Height Percent

   1   1.473           0        0.0619          -0.0000          0.2528
   2  20.513      118703        1.0670 V         2.9558          4.3589
   3  21.018     3897253       23.3492          97.0442         95.3883

     3 Peaks > Area Reject       4015956 Total Area
     3 Peaks > Height Reject      24.478 Total Height
```