Synthetic Communications

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

Montmorillonite Clay Catalysis. VIII. Synthesis of Arylcholestenes by Friedelcrafts Reaction Catalysed by Montmorillonite K-10.

Li-Jun Li , Bo Lu , Tong-Shuang Li & Ji-Tai Li

To cite this article: Li-Jun Li , Bo Lu , Tong-Shuang Li & Ji-Tai Li (1998) Montmorillonite Clay Catalysis. VIII. Synthesis of Arylcholestenes by Friedelcrafts Reaction Catalysed by Montmorillonite K-10., Synthetic Communications, 28:8, 1439-1449, DOI: 10.1080/00397919808006843

To link to this article: http://dx.doi.org/10.1080/00397919808006843

Published online: 22 Aug 2006.

SYNTHETIC COMMUNICATIONS, 28(8), 1439-1449 (1998)

MONTMORILLONITE CLAY CATALYSIS. PART 8.[1] SYNTHESIS OF ARYLCHOLESTENES BY FRIEDEL-CRAFTS REACTION CATALYSED BY MONTMORILLONITE K-10.

Li-Jun LI, Bo LU**, Tong-Shuang LI* & Ji-Tai LI

Department of Chemistry, Hebei University, Baoding 071002, Hebei, China.

Abstract: A series of 3β-arylcholestenes were synthesised by Friedel-Crafts reaction of cholesterol with arenes catalysed by montmorillonite K-10.

Friedel-Crafts alkylation is a widely used reaction for preparation of a variety of aromatic compounds.[2] The alkylating agents are usually alcohols, halides and alkenes. As to the catalysts, except for traditional Lewis acid such as $AlCl_3$, recently developed montmorillonite clays have been extensively used for this reaction.[3-10] However, alcohol alkylating agents with a steroidal skeleton have received very little attention. Recently, Sieskind and Albrecht reported the arylation of cholestanol and cholesterol with benzene to give 3β-phenylcholestane and 3β-phenylcholestenes respectively.[11] The structure and stereochemistry of the products were assigned by NMR studies. However, they did not report any spectral data of those products in their preliminary

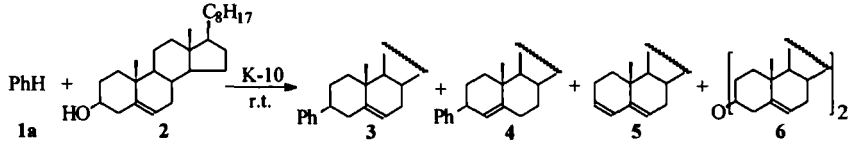
* To whom correspondence should be addressed.

** Visiting scholar from Department of Chemistry, Cangzhou Normal College.

communication.[11] Arylsterenes may be useful liquid crystals[12] and the formation of arylsterenes under catalysis of mineral clays may also have geochemical interest.[11,13] Furthermore, as a novel kind of steroid, arylsterenes might have biological activities. For these reasons, we report here the scope and limitation of the cholesterylation of arenes catalysed by montmorillonite K-10.

Results and discussion

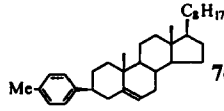
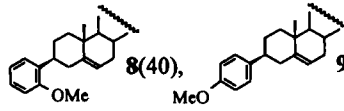
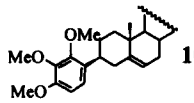
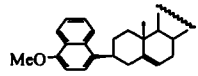
As shown in Table 1, in the presence of montmorillonite K-10, several arenes (**1a**~**1e**) when treated with cholesterol (**2**) to give the corresponding arylcholestenes (**3**, **4**, **7**~**11**). The reactions were completed within 9~36 h.



Scheme 1

The reaction of benzene (**1a**) with cholesterol (**2**) provided a complicated mixture from which 3β-phenylcholest-5-ene (**3**, yield 58%), 3β-phenylcholest-4-ene (**4**, 3.4%), cholesta-3,5-diene (**5**, 4.4%) and 3β,3'β-dicholesteryl ether (**6**, 18%) were isolated and identified (Scheme 1). Although Sieskind and Albrecht reported the same reaction was completed within 30 min,[11] we found it required a quite long time (31 h). Compounds **5** and **6** were identified by their ^{1}H NMR spectra, melting points and comparison with authentic samples.[14,15] In a previous publication, we shown that disteryl ethers could be obtained in high yield by heating sterols with K-10 in refluxing dichloromethane.[15] The structure of **3** was unambiguously identified by Sieskind and Albrecht.[11] Although from our result of the ^{1}H NMR spectrum (80 MHz) of **3**, the stereochemistry at C-3 was not

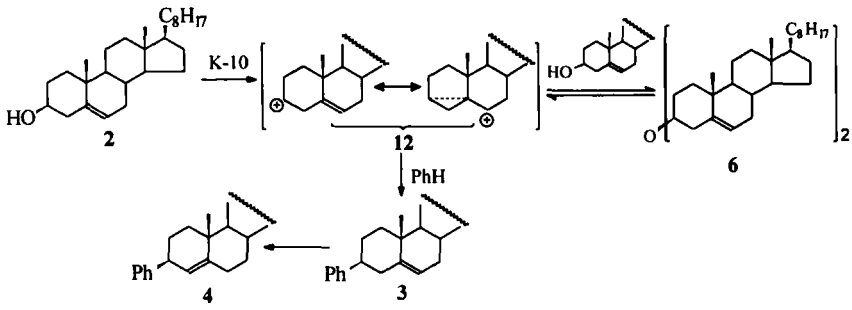
Table 1 Arylation of cholesterol catalysed by montmorillonite K-10

Entry	ArH	Time (h)	Temp. (℃)	Product (Yield%)
1a		31	r.t.(26)	**3**(58), **4**(3.4), **5**(4.4), **6**(18)
1b		36	r.t.	 **7**(35), **5**(3.9), **6**(39)
1c		12	45-50	 **8**(40), **9**(34), **5**(1), **6**(15)
1d		12	50-55	 **10**(59), **5**(3.0), **6**(27)
1e		9	50	 **11**(44), **5**(5.5), **6**(trace)

assigned clearly, benzene ring occupied an axial position at C-3 was almost impossible. However, the ^{1}H NMR spectrum (80 MHz) of **4** clearly indicated that the stereochemistry at C-3 was 3β-phenyl, since the 3-H showed a multiple signal at δ 3.25 ($W_{1/2}$=15 Hz) ppm.

A probable mechanism for the formation of **3** and **4** involves generation of a carbonium ion (**12**) both from **2** and **6** (Scheme 2).[15] Because, at the same conditions, 3β-phenylcholest-5-ene (**3**) was also obtained by using dicholesteryl ether (**6**) as substrate instead of cholesterol.

Under catalysis of K-10, the reaction of cholesterol (**2**) with toluene (**1b**) proceeded slower (36 h) at room temperature. 3β,3'β-Dicholesteryl ether (**6**, 39%) and 3β-(4'-methylphenyl)cholest-5-ene (**7**, 35%) were the main products with trace cholesta-3,5-diene (**5**, 3.9%). A strong adsorption in the infrared



Scheme 2

spectrum of **7** at 813 cm^{-1} indicated a 1,4-disubstituted benzene ring structure.

Cholesterylation of anisole progressed even slower at room temperature (48 h) and **6** was the principal product (yield 65%) with only minor 3β-(2′-methoxyphenyl)cholest-5-ene (**8**, 13%) and 3β-(4′-methoxyphenyl)cholest-5-ene (**9**, 9%). When the mixture was heated at 45～50 °C, however, the reaction could be completed in 12 h. Compounds **8** and **9** were obtained in high yield (40% and 34% respectively) with minor **6** (15%) and trace **5** (1%). The multiple signal in the ^1H NMR spectrum of **8** at 6.80～7.27 ppm and a strong adsorption in the infrared spectrum of **8** at 747 cm^{-1} implied a 1,2-disubstituted benzene ring structure. Whereas a AB system in the ^1H NMR spectrum of **9** at 6.85(2H, d, J_{AB}=8.7 Hz) and 7.15(2H, d, J_{AB}=8.7 Hz) ppm and a strong adsorption in the infrared spectrum of **9** at 826 cm^{-1} demonstrated a 1,4-disubstituted benzene ring structure. This result indicated that even for a large carbonium ion such as a steroid at C-3, the Friedel-Crafts alkylation of anisole still mainly provided *ortho*-substitution product.

It is very interesting that cholesterylation of 1,2,3-trimethoxybenzene (**1d**) at 50～55 °C provided crowded 3β-(2′,3′,4′-trimethoxyphenyl)cholest-5-ene (**10**, 59%) with minor **6** (27%) and trace **5** (3%). Whereas 3β-(3′,4′,5′-

trimethoxyphenyl)cholest-5-ene was not obtained. The ^{13}C NMR spectrum and elemental analysis of **10** indicated its purity was acceptable. The assignment of δ_C were based on DEPT experiment and on comparison with literature data of cholesterol,[16] isopropylbenzene and anisole.[17] Although the methoxyl signals at 3.84(3H, s) and 3.86(6H, s) ppm in the ^1H NMR spectrum of **10** shown the structure might be 3β-(3′,4′,5′-trimethoxyphenyl)cholest-5-ene, a AB system at 6.65(1H, d, J_{AB}=8.7 Hz) and 6.89(1H, d, J_{AB}=8.7 Hz) ppm unambiguously indicated the structure with a 1,2,3,4-tetrasubstituted benzene ring. An adsorption in the infrared spectrum of **10** at 802 cm^{-1} and no adsorption in the range of 840～900 cm^{-1} supported this conclusion.

Cholesterylation of α-methoxynaphthalene (**1e**) at 50～55 °C provided 3β-(4′-methoxy-1′-naphthyl)cholest-5-ene (**11**, 44%) with minor **6** (28%) and **5** (6%). The identity of **11** was confirmed by its ^{13}C NMR spectrum and elemental analysis. The δ_C data were assigned by DEPT experiment and by comparison with literature data of cholesterol,[16] α-methoxynaphthalene[18] and α-ethylnaphthalene.[19] This time the stereochemistry of C-3 in **11** could be assigned clearly by its ^1H NMR spectrum (400 MHz) as the 3-H shown a multiple at δ 3.236 ($W_{1/2}$=26 Hz). The signals at δ 6.789(1H, d, J=8.0 Hz), 7.317(1H, d, J=8.0 Hz), 7.445～7.538(2H, m), 8.037(1H, d, J=8.4 Hz), and 8.310(1H, d, J=8.0 Hz) ppm indicated a 1,4-disubstituted naphthalene in the molecule.

The reactions could be accelerated by raising temperature, however, the ratio of the by product, cholesta-3,5-diene (**5**), increased as well.

Arenes with electron withdrawing group, e.g. nitrobenzene, chlorobenzene, bromobenzene and even diphenyl ether failed for this reaction. In these cases only small amounts of cholesta-3,5-diene (**5**) was monitored by TLC after treatment of these compounds with cholesterol and K-10 for 7～12 h without detectable formation of arylated cholestenes. Arylamines, e.g. aniline, *N,N*-

dimethylaniline and acetanilide were also failed to give corresponding cholestenes under these conditions.

In conclusion, we have provided a convenient method for the preparation of 3β-arylcholestenes by Friedel-Crafts cholesterylation of arenes catalysed by montmorillonite K-10. This reaction are efficient for benzene or arenes with activiting groups but not for arenes with electron withdrawing groups and arylamines.

Experimental

All melting points (m.p.) were uncorrected. Elemental analyses were determined on a Carlo Erba-1106 instrument. Infrared (IR) spectra were recorded on a Perkin-Elmer 983G spectrometer. ^{1}H and ^{13}C NMR spectra were measured on Bruker AC-80 and Bruker AM-400 spectrometers using $CDCl_3$ as solvent and tetramethlysilane (TMS) as internal reference. Mass spectra were obtained on a VG-7070E spectrometer, EI, 70 eV.

The liquid arenes were used as both reagent and solvent. For solid arenes, $CHCl_3$ or hexane was employed as solvent. All reactions were carried out under anhydrous conditions. Montmorillonite K-10 was activated at 120 °C overnight before use. The ratio of K-10 to cholesterol was 5/1 (w/w). The progress of the reactions was monitored by TLC.

3β-Phenylcholest-5-ene (3) and 3β-phenylcholest-4-ene (4)

K-10 Catalyst (2.5 g) was added to a solution of cholesterol (**2**, 500 mg, 1.29 mmol) in benzene (**1a**, 60 ml, dried by azeotropic distillation). The mixture was stirred at room temperature for 31 h. The catalyst was separated by filtration over a bed of silica gel and washed with diethyl ether, the solvent was evaporated under reduced pressure to give a light yellow solid. The crude product was chromatographied on silica gel (200 ~ 300 mesh) impregnated with

10% silver nitrate,[20] eluted with petroleum ether (b.p. 60-90 °C) and the mixture of petroleum ether and benzene (50:1, v/v) to afford cholesta-3,5-diene (**5**, 21 mg, yield 4.4%), 3β-phenylcholest-4-ene (**4**, 19.6 mg, 3.4%), 3β-phenylcholest-5-ene (**3**, 335 mg, 58%) and 3β,3'β-dicholesteryl ether (**6**, 88 mg, 18%) successively. **3**, m.p. 153-4 °C (colourless needles from petroleum ether/acetone). ν_{max}(KBr): 3085, 3025, 1602, 1491, 1464 cm^{-1}. δ_H(80 MHz): 0.70(3H, s, 18-H), 0.87(6H, d, J=6.0 Hz, 26,27-H), 0.93(3H, d, J=6.0 Hz, 21-H), 1.08(3H, s, 19-H), 5.35(1H, d, J=4.5 Hz, 6-H), 7.25(5H, s, Ar-H) ppm. m/z(%): 446(100, M^+), 431(56), 333(16), 301(22), 275(23), 91(38). **4**, m.p. 119-23 °C (colourless needles from acetone). ν_{max}(KBr): 3024, 2933, 2867, 1465, 1377 cm^{-1}. δ_H(80 MHz): 0.70(3H, s, 18-H), 0.87(6H, d, J=6.0 Hz, 26,27-H), 0.92(3H, d, J=6.0 Hz, 21-H), 1.10(3H, s, 19-H), 3.25(1H, m, $W_{1/2}$=15 Hz, 3α-H), 5.29(1H, brs, 4-H), 7.21(5H, brs, Ar-H) ppm. m/z(%): 446(100, M^+), 431(48), 328(66), 287(26), 215(17), 157(69), 91(60). **5**, m.p. 78-79 °C, lit.[14] 79-80 °C. **6**, m.p. 198-201 °C, lit.[15] 200-203 °C.

3β-(4'-Methylphenyl)-cholest-5-ene (7)

The same procedure as described above was repeated by employing toluene (**1b**, dried by azeotropic distillation) as reactant and solvent. After stirring at r.t. for 36 h and workup, cholesterol (500 mg) gave **5** (19 mg, 3.9%), 3β-(4'-methylphenyl)cholest-5-ene (**7**, 209 mg, 35%) and **6** (190 mg, 39%). **7**, m.p. 160-162 °C (colourless needles from acetone/petroleum ether). ν_{max}(KBr): 3046, 3016, 1513, 1464, 1375, 812, 526 cm^{-1}. δ_H (80 MHz): 0.70(3H, s, 18-H), 0.87(6H, d, J=6.0 Hz, 26,27-H), 0.93(3H, d, J=6.0 Hz, 21-H), 1.08(3H, s, 19-H), 2.32(3H, s, Ar-CH_3), 5.36(1H, d, J=4.4 Hz, 6-H), 7.12(4H, s, Ar-H). m/z: 460(M^+, 100), 445(56), 329(14), 301(20), 275(20), 157(18), 105(57).

3β-(2'-methoxyphenyl)cholest-5-ene (8) and 3β-(4'-methoxyphenyl)cholest-5-ene (9)

A mixture of K-10 catalyst (2.5 g), cholesterol (**2**, 500 mg) and anisole (**1c**, 40 ml) was heated at 45～50°C on an oil bath under stirring for 12 h. After the same workup as described for **3** and **4**, the crude product was chromatographied on silica, eluted by petroleum ether and the mixture of petroleum ether-diethyl ether(50:1, v/v) to give **5** (5 mg, 1%), **6** (73 mg, 15%), 3β-(2'-methoxyphenyl)cholest-5-ene (**8**, 247 mg, 40%) and 3β-(4'-methoxyphenyl)cholest-5-ene (**9**, 210 mg, 34%) successively. **8**, m.p. 125-127.5 °C (colourless needles from acetone). ν_{max}(KBr): 3062, 3026, 2934, 2850, 1598, 1493, 1465, 1248, 1053, 747 cm^{-1}. δ_H(80 MHz): 0.70(3H, s, 18-H), 0.87(6H, d, J=6.0 Hz, 26,27-H), 0.93(3H, d, J=6.0 Hz, 21-H), 1.08(3H, s, 19-H), 3.81(3H, s, 2'-OCH_3), 5.35(1H, m, 6-H), 6.80～7.27(4H, m, Ar-H) ppm. m/z: 476(100, M^+), 461(39), 363(6), 329(16), 301(11), 275(9), 215(11), 187(28), 175(25), 135(38), 121(60), 91(28). **9**, m.p. 125-126°C (colourless needles from acetone). ν_{max}(KBr): 3063, 3029, 2930, 1611, 1511, 1463, 1377, 1257, 1238, 1176, 1039, 826, 802, 536 cm^{-1}. δ_H(80 MHz): 0.70(3H, s, 18-H), 0.87(6H, d, J=6.0 Hz, 26,27-H), 0.94(3H, d, J=6.0 Hz, 21-H), 1.07(3H, s, 19-H), 3.78(3H, s, 4'-OCH_3), 5.35(1H, d, J=4.2 Hz, 6-H), 6.85(2H, d, J_{AB}=8.7 Hz, 3',5'-H), 7.15(2H, d, J_{AB}=8.7 Hz, 2',6'-H) ppm. m/z(%): 476(100, M^+), 461(16), 329(48), 275(8), 215(6), 147(57), 134(58), 121(50), 95(22).

3β-(2',3',4'-trimethoxyphenyl)cholest-5-ene (10)

A mixture of 1,2,3-trimethoxybenzene (**1d**, 510 mg, 3.03 mmol), cholesterol (**2**, 500 mg, 1.29 mmol), K-10 (2.5 g) and chloroform (15 ml) was heated at 50～55°C on an oil bath under stirring for 12 h. The same workup as described above was applied to provide **5** (14 mg, 3.0%), **6** (132 mg, 27%) and 3β-(2',3',4'-trimethoxyphenyl)cholest-5-ene (**10**, 410 mg, 59%). **10**, m.p. 128-130 °C (colourless platelets from acetone). Calculated for $C_{35}H_{56}O_3$: C, 80.54%; H,

10.51%. Found: C, 80.30%; H, 10.50%. ν_{max}(film): 2940, 2870, 1595, 1490, 1460, 1410, 1375, 1278, 1098, 1048, 1020, 802, 700 cm^{-1}. δ_H(80 MHz): 0.70(3H, s, 18-H), 0.87(6H, d, J=6.1 Hz, 26,27-H), 0.93(3H, d, J=6.0 Hz, 21-H), 1.08(3H, s, 19-H), 2.84(1H , m, $W_{1/2}$=26 Hz, 3α-H), 3.84(3H, s, -OCH_3), 3.86(6H, s, 2 x -OCH_3), 5.32(1H, m, 6-H), 6.65(1H, d, J_{AB}=8.7 Hz, 5'-H), 6.89(1H, d, J_{AB}=8.7 Hz, 6'-H) ppm. δ_C(100 MHz): 39.99(1), 29.67(2), 38.49(3), 40.10(4), 142.21(5), 120.77(6), 31.94(7), 31.94(8), 50.46(9), 36.98(10), 20.95(11), 28.25(12), 42.34(13), 56.86(14), 24.31(15), 39.86(16), 56.17(17), 11.89(18), 19.64(19), 35.80(20), 18.73(21), 36.20(22), 23.83(23), 39.52(24), 28.01(25), 22.56(26), 22.81(27), 133.12(1'), 151.51(2' or 4'), 143.20(3'), 151.66(4' or 2'), 107.31(5'), 119.90(6'), 55.97(-OCH_3), 60.69(-OCH_3), 61.28(-OCH_3) ppm. m/z(%): 536(72, M^+), 521(4), 329(6), 207(100), 176(52).

3β-(4'-methoxy-1'-naphthyl)cholest-5-ene (11)

A mixture of α-methoxynaphthalene (**1e**, 290 mg, 1.84 mmol), cholesterol (**2**, 313 mg, 0.811 mmol), K-10 (1.5 g) and cyclohexane (20 ml) was stirred at 50 °C on an oil bath for 9 h. The same workup as described above was applied to give **5** (16 mg, 5.5%), **6** (trace) and 3β-(4'-methoxy-1'-naphthyl)cholest-5-ene (**11**, 188 mg, 44%). **11**, m.p. 195.5-196.5 °C (colourless needles from ethyl acetate). Calculated for $C_{38}H_{54}O$: C, 86.63%; H, 10.33%. Found: C, 86.33%; H, 10.51%. ν_{max}(KBr): 3075, 2940, 2876, 1618, 1590, 1460, 1380, 1270, 1235, 1150, 1095, 805, 755 cm^{-1}. δ_H(400 MHz): 0.708(3H, s, 18-H), 0.871, 0.875 (6H, 2d, J=6.5 Hz, 26,27-H), 0.936(3H, d, J=6.4 Hz, 21-H), 1.116(3H, s, 19-H), 3.236(3H, m, $W_{1/2}$=26 Hz, 3α-H), 3.984(3H, s, -OMe), 5.399(1H, d, J=4.7 Hz, 6-H), 6.789(1H, d, J=8.0 Hz, 3'-H), 7.317(1H, d, J=8.0 Hz, 2'-H), 7.445~7.538(2H, m, 6',7'-H), 8.037(1H, d, J=8.4 Hz, 8'-H), 8.310(1H, d, J=8.0 Hz, 5'-H) ppm. δ_C(100 MHz): 40.35(1), 29.76(2), 40.19(3), 40.57(4),

143.42(5), 121.75(6), 31.99(7), 31.99(8), 50.62(9), 37.29(10), 21.01(11), 28.27(12), 42.37(13), 56.90(14), 24.33(15), 39.89(16), 56.20(17), 11.91(18), 19.79(19), 35.82(20), 18.76(21), 36.23(22), 23.85(23), 39.55(24), 28.03(25), 22.58(26), 22.83(27), 134.81(1'), 120.04(2'), 103.43(3'), 153.61(4'), 122.63, 123.03, 124.67(5', 6', 7'), 126.22(8'), 132.26(9'), 125.91(10'), 55.45(-OMe). m/z: 526(100, M^+), 511(2), 329(2), 197(89), 171(16), 165(6), 95(9).

Acknowledgements: The project was supported by the NSFC (29572039), the Education Commission of Hebei Province and the Science and Technology Commission of Hebei Province.

References

1. Part 7: Li, T. S.; Zhang, Z. H.; Yang, F. and Fu, C. G. *J. Chem. Res.(S),* **1997**, (in press).
2. Roberts, R. M. and Khalaf, A. A. "Friedel-Crafts alkylation chemistry," Marcel Dekker, New York, **1984**.
3. Chalais, S.; Cornelis, A.; Gerstmans, A.; Kolodziejski, W.; Laszlo. P.; Mathy, A. and Metra, P. *Helv. Chim. Aata*, **1985**, *68,* 1196.
4. Laszlo, P. and Mathy, A. *Helv. Chim. Aata*, **1987**, *70*, 577.
5. Saib, D. and Foucaud, A. *J. Chem. Res.(S)*, **1987**, 372-373.
6. Clark, J. H.; Kybett, A. P.; Macquarrie, D. J.; Barlow, S. J. and Landon, P. *J. Chem. Soc., Chem. Commun.* **1989**, 1353.
7. Cornelis, A.; Dony, C.; Laszlo, P. and Nsunda, K. M. *Tetrahedron Lett.* **1991**, *32*, 2901.
8. Cornelis, A.; Laszlo, P. and Wang, S. F. *Tetrahedron Lett.* **1993**, *34*, 3849.
9. Tateiwa, J. I.; Horiuchi, H.; Suama, M. and Uemura, S. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2883.
10. Li, T. S. and Jin, T. S. *Youji Huaxue,* **1996**, *16*, 385.
11. Sieskind, O. and Albrecht, P. *Tetrahedron Lett.* **1993**, *34*, 1197.

12. Hibert, M. and Solladie, G. *Mol. Cryst. Liq. Cryst.* **1981**, *64*, 211.

13. Williams, J. A.; Dolcater, D. L.; Torkelson, B. E. and Winters, J. C. *Org. Geochem.* **1988**, *13*, 47.

14. D'Onfrio, F. and Scettri, A. *Synthesis,* **1985**, 1159.

15. Li, T. S.; Li, H. Z.; Guo, J. L. and Jin, T. S. *Synth. Commun.* **1996**, *26*, 2497.

16. Reich, H. J.; Jautelat, M.; Messe, M. T.; Weigert, F. J. and Roberts, J. D. *J. Am. Chem. Soc.* **1969**, *91*, 7445.

17. Yu, D. Q.; Yang, J. S. and Xie, J. X. "*Handbook of Analytical Chemistry, Vol. 5, Nuclear Magnetic Resonance Spectroscopy* (in Chinese)," Chemical Industry Press, Beijing, **1989**, pp 465-466.

18. Sadtler Research Laboratories, INC, "*Sadtler Standard Carbon-13 NMR Spectra*," **1978**, vol. 32, 6243C.

19. Sadtler Research Laboratories, INC, "*Sadtler Standard Carbon-13 NMR Spectra,*" **1978**, vol. 8, 1470C.

20. Li, T. S.; Li, J. T. and Li, H. Z. *J. Chromatogr. A,* **1995**, *715*, 372.

(Received in the UK 30 September 1997)