Asymmetric α-Alkylation of α,β-Unsaturated Esters. Application to the Synthesis of (R)-Lavandulol, (R)-Sesquilavandulol and Related Trifluoromethyl Compounds

S. Faure, O. Piva*

UMR 6519 C.N.R.S. "Réactions sélectives et applications", UFR Sciences - Université de Reims - Champagne - Ardenne

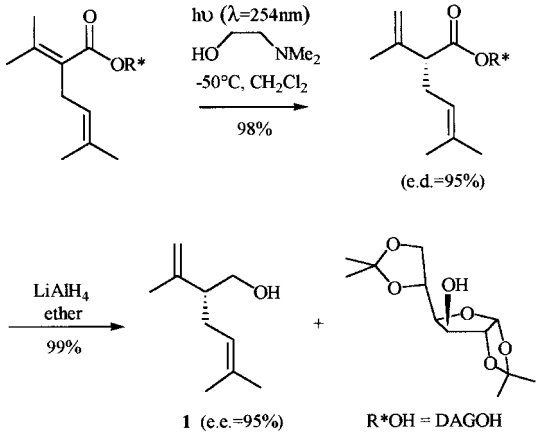
B.P. 1039 - 51687 Reims cedex - France

Fax 00 33 (0)3 26 05 31 66 ; e-mail olivier.piva@univ-reims.fr.

Received 5 August 1998

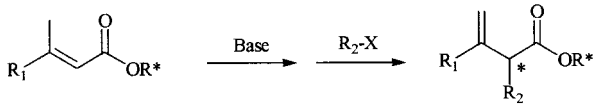
Abstract: Diastereoselective α-alkylation/deconjugation of esters of diacetone D-glucose has been performed and applied to the syntheses of (R)-lavandulol, (R)-sesquilavandulol with de up to 74%. The same reaction performed with trifluoromethyl derivatives was also achieved but without significant diastereoselectivity.

Some years ago, we reported the synthesis of (R)-Lavandulol **1** using a highly diastereoselective photoisomerization of a α,β-unsatured ester[1] using as chiral moiety the cheap and commercially available diacetone D-glucose[2] (DAG-OH) (Scheme 1).



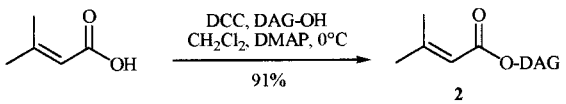
Scheme 1

While this powerful method appeared difficult to scale up, we decided recently to carry out an alternative approach to lavandulol and other terpene alcohols based on the diastereoselective alkylation of α-unsubstituted-α,β-unsaturated esters bearing the same chiral alkoxy group (Scheme 2).



Scheme 2

3,3-Dimethyl acrylic acid was easily transformed into the diacetone D-glucose ester **2** in 91 % using DCC activation[3] (Scheme 3).



Scheme 3

The diastereoselective alkylations were performed under different experimental conditions changing the nature of the base and solvents. Results are summarized in table 1.

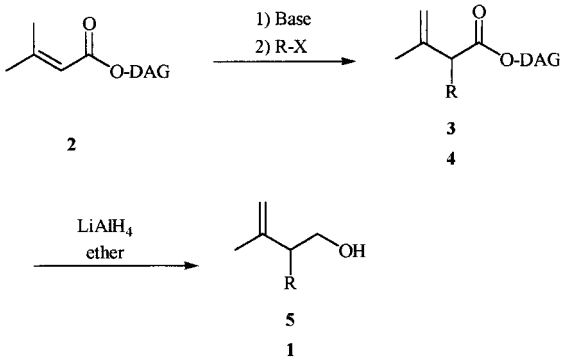
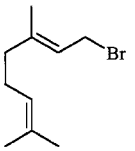
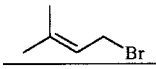


Table 1. Diastereoselective alkylation of ester **2**

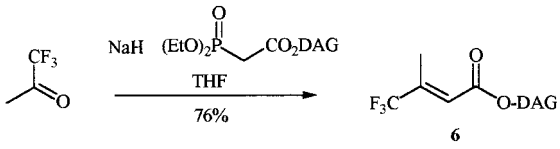
R-X	Base	Solvent / additive	β,γ-unsaturated ester Yield	de[a]	conf.	Alcohol
	LDA	THF	**3** 35%	58%	(R)[b]	
	NaHMDS	THF	**3** 67%	74%	(R)[b]	**5** 80%
	NaHMDS	THF + HMPA (3eq)	**3** 53%	58%	(R)[b]	
	NaHMDS	THF	**4** 59%	73%	(R)[c]	**1** 85%

a) de measured on ^{1}H - NMR spectrum of the crude mixture.
b) Configuration established after reduction to the parent alcohol and by comparison with data of the literature.
c) Configuration established by comparison with spectra recorded using the photochemical isomerization (scheme 1 - ref. 1)

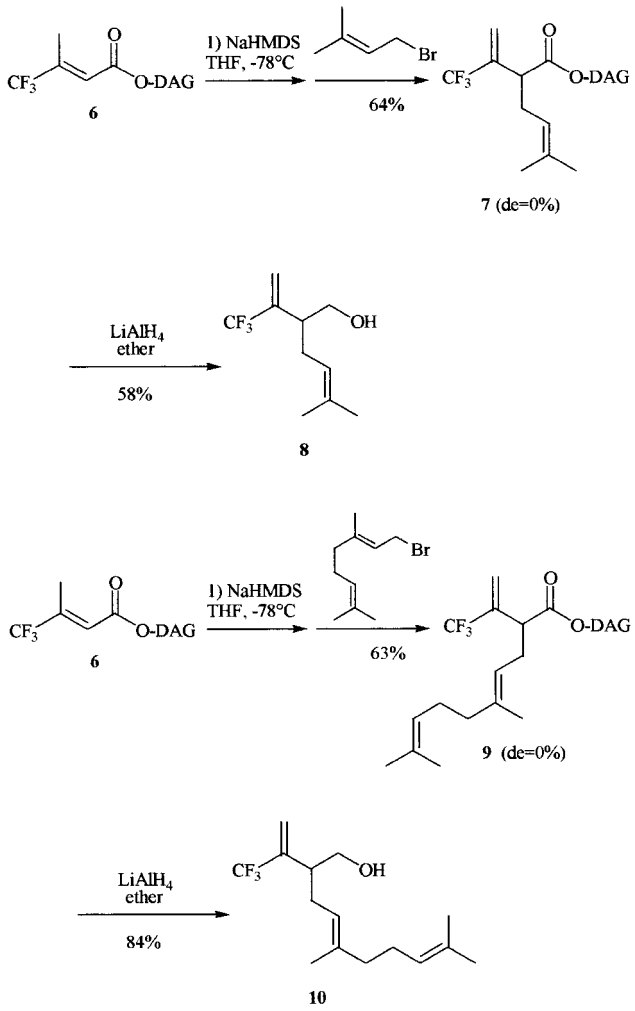
According to table 1, NaHMDS seems the more suitable base to obtain the monoalkylated compound in convenient yields and acceptable de (up to 74%). When LDA was used, diastereoselectivity was significantly lower as well as the efficiency of the process. The low yield measured could result from the formation of a vinylketene and DAG-OH as it has been already pointed out for similar alkylations of sugar esters[4,5]. Finally, the β,γ-unsaturated esters **3** and **4** were respectively reduced by $LiAlH_4$ into (R)-sesquilavandulol **5** and (R)-lavandulol **1** according a previous procedure[1]. In order to develop an access to trifluoromethyl analogues of **1** on **5** which could exhibit new fragrance properties or biological activities,[6] we have submitted to the same alkylation conditions ester **6** obtained in high yield from 3,3,3-trifluoroacetone by a Wittig-Horner reaction[7] (Scheme 4).

The alkylation occurred in good yields but without diastereoselectivity (Scheme 5).

By comparison with the non fluorinated compounds, the lack of selectivity observed for **6** could be due to an increase of the acidity of the proton in α-position of the carboxylic group in **7** and **9**. Such an

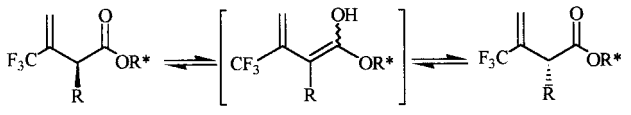


Scheme 4



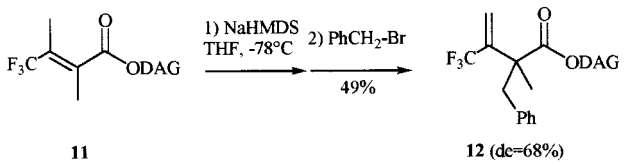
Scheme 5

increase of acidity by the withdrawing electron group CF_3 has been already observed for related esters[8]. In the case of **7** and **9**, an epimerization could occur rapidly leading to the formation of a 1:1 mixture of diastereoisomers (Scheme 6).



Scheme 6

This hypothesis has been confirmed by examining the α-alkylation of ester **11** which is already substituted by one alkyl group on carbon 2 (Scheme 7).



Scheme 7

The reaction delivered **12** in moderate yield but with a very similar level of diastereoselectivity observed with ester **2**. It is noteworthy that such a process allows the preparation of compounds with a quaternary chiral center[9].

In conclusion, we have developed an alternative and efficient reaction to prepare by diastereoselective alkylation (R)-lavandulol and (R)-sesquilavandulol with de up to 74%. We have also been able to prepare for the first time trifluoroanalogues of these two terpenes but without significant enantioselectivities due to an easy racemization of the new chiral center. However, the isomerisation procedure described therein allows the preparation of terminal alkenes bearing one trifluoromethyl group at an internal position. In the non fluorinated serie, work is now underway to increase the diastereoselectivity by changing the nature of the sugar moiety and also to generalize this reaction to the synthesis of chiral compounds especially those bearing quaternary centers.

Acknowledgments : S.F. warmly thanks M.E.N.R.T for a grant.

References and notes

(1) Piva, O. *J. Org. Chem*. **1995**, *60*, 7879 and references therein.

(2) For a recent review on chiral induction by carbohydrates : Hultin, P.G. ; Earle, M.A. ; Sudharshan, M. *Tetrahedron* **1997**, *53*, 14823.

(3) Neises, B. ; Steglich, W. *Angew. Chem. Int. Ed. Engl*. **1978**, *17*, 522.

(4) Kunz, H.; Mohr, J. *J. Chem. Soc., Chem. Commun*. **1988**, 1315.

(5) Mulzer, J.; Hiersemann, M.; Buschmann, J.; Luger, P. *Liebigs Ann.* **1996**, 649.

(6) a) Nagai, T.; Ohtsuka, H.; Koyama, M.; Ando, A.; Miki, T. Kumadaki, I. *Heterocycles* **1992**, *33*, 51. b) Patani, G.A.; La Voie, E.J. *Chem. Rev.* **1996**, 3147. c) Prié, G.; Thibonnet, J.; Abarbri, M.; Duchêne, A.; Parrain, J.L. *Synlett* **1998**, 839. d) Peng, S.; Qing, F-L.; Guo, Y. *Synlett* **1998**, 859.

(7) a) Zhu, C.D. ; Van Lancker, B ; Van Haver, D. ; De Clercq, P.J. *Bull. Soc. Chim. Belg*. **1994**, *103*, 263. b) Nemoto, H. ; Satoh, A. ; Fukumoto, K. ; Kabuto, C. *J. Org. Chem.* **1995**, *60*, 594.

(8) Schlosser, M. *Angew. Chem. Int. Ed. Engl*. **1998**, *37*, 1496.

(9) a) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037. b) Jung, M.E.; D'Amico, D.C. *J. Am. Chem. Soc*. **1995**, *117*, 7379. c) Mino, T.; Takagi, K.; Yamashita, M. *Synlett* **1996**, 645. d) Yamamoto, Y.; Hara, S.; Suzuki, A. *Synlett* **1996**, 883. e) Enders, D.; Backhaus, D.; Runsink, J. *Tetrahedron* **1996**, *52*, 1503. f) Yang, X.; Wang, R. *Tetrahedron: Asymmetry* **1997**, *8*, 3275. g) Alves, J.C.F.; Simas, A.B.C.; Costa, P.R.R.; d'Angelo, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1963. h) Belokon', Y.N.; Kotchetkov, K.A.; Churkina, T.D.; Ikonnikov, N.S.; Chesnokov, A.A.; Larionov, O.V.; Parmar, V.S.; Kumar, R.; Kagan, H.B. *Tetrahedron: Asymmetry* **1998**, *9*, 851.

(10) **Typical experimental procedure for the alkylation step**: To a solution of ester (2.5 mmol) in THF (25 ml) under argon was added at -78°C a 1.0M THF solution of sodium bis(trimethylsilyl)amide (2.75 ml). The resulting mixture was

stirred at this temperature for 2 hours. The bromide (2.75 mmol) previously dissolved in THF (2 ml) was dropwise added via syringe. The solution was stirred for an additional time of 3 hours at -78°C and subsequently quenched with brine (10 ml). After extraction with ether (3 x 20 ml), the organic layers were dried over $MgSO_4$, concentrated under vacuum and the alkylated product was purified by flash-chromatography (hexane : ethyl of acetate / 93:7).

All new compounds gave satisfactory spectroscopic and analytical data. ^{19}F NMR spectra were measured relative to $CFCl_3$. Selected data of **2**: Colorless oil ^1H-NMR (250 MHz, $CDCl_3$): δ 1.30 (3H,s); 1.31 (3H, s); 1.41 (3H, s); 1.52 (3H, s); 1.91 (3H, s); 2.18 (3H, s); 4.01-4.09 (2H, m); 4.15-4.35 (2H, m); 4.50 (1H, d, J = 3.7 Hz); 5.26 (1H, d, J = 2.4 Hz); 5.67 (1H, t, 1.1 Hz); 5.86 (1H, d, 3.7 Hz). ^{13}C-NMR (62.5 MHz, $CDCl_3$): 20.3; 25.3; 26.2; 26.7; 27.4; 66.9; 72.6; 75.3; 79.7; 83.5; 105.0; 109.1; 112.1; 115.1; 158.8; 164.9. IR ($CHCl_3$): 1730 and 1655 cm^{-1}. $[\alpha]^{21}_D$ = -46 (1.0, $CHCl_3$). Analysis calcd for $C_{17}H_{26}O_7$: C 59.63%, H 7.65%. Found: C 60.02%, H 7.85%.

3: ^1H-NMR (250 MHz, $CDCl_3$): δ 1.28 (3H, s); 1.29 (3H, s); 1.39 (3H, s); 1.54 (3H, s); 1.58 (3H, s); 1.62 (3H, s); 1.67 (3H, s); 1.74 (3H, s); 1.92-2.10 (4H, m); 2.30 (1H, ddd, J = 7.7 Hz, J = 7.5 Hz, J = 14.9 Hz); 2.52 (1H, ddd, J = 7.7 Hz, J = 7.5 Hz, J = 14.9 Hz); 3.05 (1H, t, 7.7 Hz); 3.92-4.20 (4H, m); 4.41 (1H, d, J = 3.7 Hz); 4.90 (2H, sb); 5.01-5.10 (2H, m); 5.28 (1H, d, J = 1.7 Hz); 5.82 (1H, d, J = 3.5 Hz, minor diastereoisomer) and 5.86 (1H, d, J = 3.7 Hz, major diastereoisomer). ^{13}C-NMR (62.5 MHz, $CDCl_3$) Major diastereoisomer: δ 14.0; 16.0; 17.5; 20.0; 25.0; 25.6; 26.1; 26.5; 26.6; 28.5; 39.6; 53.2; 67.4; 70.6; 75.8; 80.2; 83.3; 105.0; 109.1; 112.2; 114.1; 120.6; 123.9; 137.3; 141.7; 171.9. MS: 478 ($M^{+\cdot}$). IR ($CHCl_3$): 1745, 1455 and 1150 cm^{-1}. $[\alpha]^{21}_D$ = -44.4 (0.9, $CHCl_3$).

6: White solid, mp= 80°C. ^1H-NMR (250 MHz, $CDCl_3$) δ 1.32 (6H, s); 1.42 (3H, s); 1.54 (3H, s); 2.28 (3H, d, J = 1.1 Hz); 3.95-4.30 (4H, m); 4.54 (1H, d, J = 3.4 Hz); 5.35 (1H, s); 5.89 (1H, d, J = 3.8 Hz); 6.33(1H, sl). ^{19}F-NMR (235 MHz, $CDCl_3$) δ -71.8. Analysis calcd for $C_{17}H_{23}O_7F_3$: C 51.51%, H 5.85%. Found: C 51.60%, H 5.79%. $[\alpha]^{21}_D$ = -45.0 (1.0, $CHCl_3$).

8: oil. ^1H-NMR (250 MHz, $CDCl_3$): δ 1.57 (O<u>H</u>, bs); 1.63 (3H, s); 1.70 (3H, s); 2.15-2.40 (2H, m); 2.51 (1H, ddt, J = 5.7 Hz, J = 5.3 Hz, J = 7.2 Hz); 3.64 (1H, dd, J = 5.3 Hz, J_{AB} = 11.0 Hz); 3.72 (1H, dd, J = 5.7 Hz, J_{AB} = 11.0 Hz); 5.09 (1H, tq, J = 7.2 Hz, J < 1 Hz); 5.45 (1H, m); 5.87 (1H, q, J = 1.5 Hz). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 17.6 (CH_3); 25.6 (CH_3); 29.5 (CH_2); 41.9 (CH); 64.2 (CH_2); 119.3 (C=CH_2); 120.9 (C=CH); 123.7 (q, $^1J_{C\text{-}F}$ = 273.6 Hz, <u>C</u>F_3); 131.9 (<u>C</u>$(CH_3)_2$); 139.1 (q, $^2J_{C\text{-}F}$ = 28 Hz, ((CF_3)<u>C</u>=CH_2). ^{19}F-NMR (235 MHz, $CDCl_3$) δ -68.3. IR ($CHCl_3$): 3600-3100, 1165 and 1120 cm^{-1}.

10: oil. ^1H-NMR (250 MHz, $CDCl_3$): δ 1.53 (O<u>H</u>, bs); 1.61 (3H, s); 1.62 (3H, s); 1.68 (3H, s); 2.03 (4H, m); 2.29 (2H, m); 2.53 (1H, ddt, J = 5.3 Hz, J = 5.7 Hz, J = 6.9 Hz); 3.64 (1H, dd, J = 5.3 Hz, J_{AB} = 9.1 Hz); 3.72 (1H, dd, J = 5.7 Hz, J_{AB} = 9.1 Hz); 5.08 (1H, tq, J = 6.9 Hz, J = 1.5 Hz); 5.11 (1H, tq, J = 6.9Hz, J < 1 Hz); 5.46 (1H, s); 5.87 (1H, d, J = 1.5 Hz). ^{13}C-NMR (62.5 MHz, $CDCl_3$) δ 16.0 (CH_3); 17.6 (CH_3); 25.6 (CH_3); 26.5 (CH_2); 29.4 (CH_2); 39.7 (CH_2); 42.0 (CH); 64.3 (CH_2); 119.3 (C=<u>C</u>H_2); 120.9 (C=<u>C</u>H); 123.8 (q, $^1J_{C\text{-}F}$ = 270 Hz, CF_3); 124.1 (C=<u>C</u>H); 131.5 (=<u>C</u>$(CH_3)_2$); 137.5 (=<u>C</u>(CH_3));139.1 (q, $^2J_{C\text{-}F}$ = 28 Hz, (CF_3)<u>C</u>=CH_2). ^{19}F-NMR (235 MHz, $CDCl_3$) δ -68.5. IR ($CHCl_3$): 3360, 1454 and 1315 cm^{-1}.