Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 10, pp. 1575–1580, 1997

Printed in Great Britain
PII: S0957-4166(97)00126-2
0957-4166/97 $17.00 + 0.00

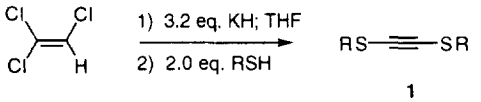
Efficient synthesis of chiral acetylene dithioethers in enantiomerically pure form

Jaume Balsells, Albert Moyano, Miquel A. Pericàs* * and Antoni Riera*

Unitat de Recerca en Síntesi Asimètrica (URSA), Departament de Química Orgànica, Universitat de Barcelona, c/ Martí i Franquès, 1-11. 08028- Barcelona, Spain

Abstract: Chiral acetylene dithioethers have been synthesized by the first time in enantiomerically pure form through a high yield (93–100%), one-pot procedure involving the successive treatment of trichloroethylene with three equivalents of lithium bis(trimethylsilyl)amide and two equivalents of a chiral thiol in diethyl ether solution.

Acetylenic dithioethers **1** are electron rich alkynes which present a high interest as synthetic intermediates.[1] Also due to the electronic nature of their triple bonds, they are promising ligands and reagents for co-ordination chemistry.[2] Some years ago, we reported a broad scope, highly efficient synthesis of these species (Scheme 1) taking place as a one-pot procedure from trichloroethylene.[3]



1

Scheme 1.

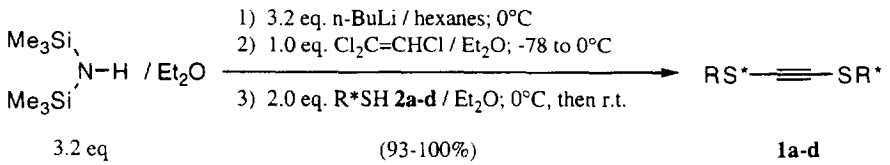
In the course of a research program devoted to the preparation of new chiral thiols and to the study of their behaviour as auxiliaries and ligands for asymmetric synthesis,[4] the preparation of chiral, non-racemic acetylenic dithioethers was planned.

Since we have observed that currently available commercial samples of potassium hydride occasionally fail to dehydrochlorinate trichloroethylene to dichloroacetylene, and this is the first step in the mechanistic pathway leading to acetylene dithioethers,[5,6] we planned to employ an alternative base for the reaction. We reasoned that the problems associated with the use of potassium hydride could have its origin in the physical state of the reagent, and that these problems would disappear when using a soluble, sufficiently strong base. Lithium bis(trimethylsilyl)amide [LiHMDS], which is very soluble in ether type solvents, thus reacting with trichloroethylene in a homogeneous manner, and has been previously used by Kende for the generation of ethereal solutions of dichloroacetylene,[7] was selected as the base for our study.

To our satisfaction, when 3.2 eq. of hexamethyldisilazane dissolved in diethyl ether were sequentially treated with n-butyllithium (3.2 eq., 0°C), trichloroethylene (1.0 eq., −78 to 0°C) and a chiral thiol **2a–d** (2.0 eq., 0°C), and the resulting mixture was stirred at room temperature for 24–48 h, the corresponding acetylene dithioethers were cleanly formed in excellent yield (Scheme 2 and Table 1)

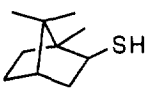
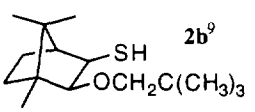
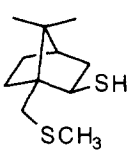
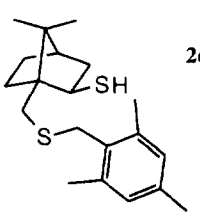
According to previous knowledge,[7] it is clear that the low temperature reaction of lithium bis(trimethylsilyl)amide with trichloroethylene generates a solution of dichloroacetylene, which exists in the presence of 2.0 eq. of excess base. Dichloroacetylene then reacts with the corresponding thiol/thiolate, most probably through two consecutive addition/elimination steps. In favour of this interpretation is the fact that the reaction with **2b** (and with **2c**), when prematurely quenched, leads

* Corresponding author. Email: mpb@ursa.qo.ub.es and are@ursa.qo.ub.es



Scheme 2.

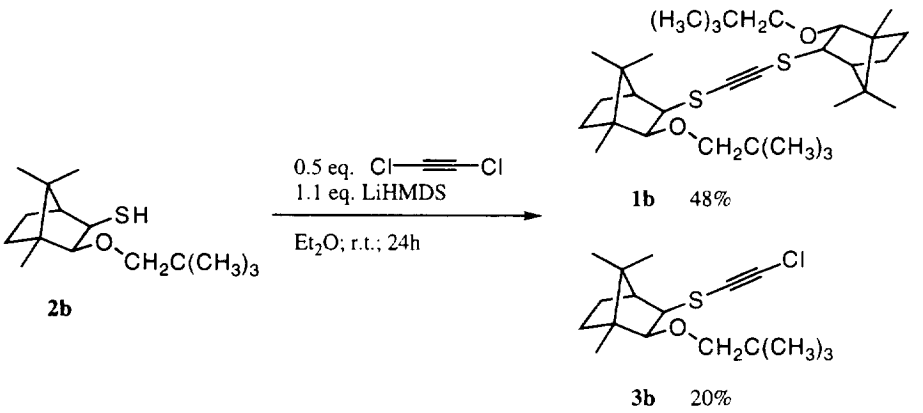
Table 1. Preparation of chiral acetylene dithioethers in enantiomerically pure form

Starting Thiol		Stirring period at r.t.	Acetylene dithioether	Yield [%]
	**2a**[8]	24h	**1a**	93
	**2b**[9]	48h[a]	**1b**	98
	**2c**[4]	48h[b]	**1c**	96
	**2d**[10]	24h	**1d**	100

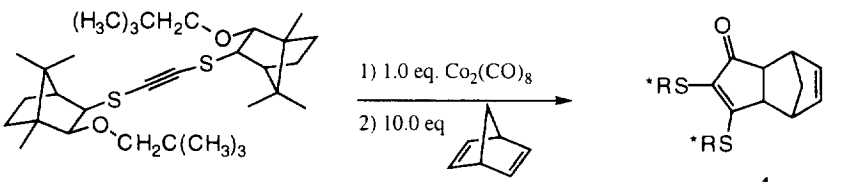
[a]When the stirring period was 24h, yield of **1b** was 48%, and the corresponding alkylthiochloroacetylene **3b** could be isolated in 20% yield. [b]When the stirring period was 24h, yield of **1c** was 78%, and the corresponding alkylthiochloroacetylene **3c** could be isolated in 22% yield.

to the isolation of substantial amounts of the corresponding alkylthiochloroacetylenes **3b** (and **3c**), as shown in Scheme 3 for **2b**.

We are currently exploring the synthetic potential of the prepared homochiral acetylene dithioethers **1a–d**. As an example, **1b** undergoes a diastereoselective Pauson–Khand reaction[11,12] with norbornadiene under both thermal and *N*-oxide promoted conditions leading to the highly functionalised tricyclic ketone **4** (Scheme 4). In this respect, it is interesting to highlight the beneficial effect on selectivity of the simultaneous presence of two alkylthio groups on the reacting alkene, since the reaction of the corresponding alkylthioacetylene with norbornadiene takes place with low (1.7:1) diastereoselectivity.[13]



Scheme 3.



Conditions	Yield	d.r.
2h, 90°C	23%	4:1
6 eq. NMO, 0°C	25%	6:1

Scheme 4.

In summary, we have developed a very simple, high yield one-pot method for the preparation of enantiomerically pure acetylene dithioethers. Work on the applications of these interesting new substances is being actively pursued in our laboratories and will be reported in due course.

Experimental section

General methods

Optical rotations were measured at room temperature (23°C) on a Perkin–Elmer 241 MC polarimeter (Concentration in g/100 ml). Melting points were determined on a Gallenkamp apparatus and have not been corrected. Infrared spectra were recorded on a Perkin–Elmer 681 instrument. NMR spectra were acquired on a Varian XL-200 instrument in $CDCl_3$. ^{1}H-NMR spectra were obtained at 200 MHz (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and b=broad) and ^{13}C-NMR spectra were obtained at 50.3 MHz. Carbon multiplicities have been assigned by DEPT experiments. Mass spectra were recorded on a Hewlett–Packard 5890 instrument at 70 eV ionising potential; ammonia was used for chemical ionisation (CI). Elemental analyses were performed by the "Servei d'Anàlisis Elementals del CSIC de Barcelona". Chromatographic separations were carried out using NEt_3 pre-treated (2.5% v/v) SiO_2 (70-230 mesh) eluting with hexanes. Chromatographic analyses were performed on a Hewlett–Packard 1050 HPLC instrument equipped with a Nucleosil 120 C18 (20 cm) column.

Preparation of 1,2-bis[(1S,2S,4S)-1,7,7-trimethylbicyclo[2.2.1]heptyl-2-thio]acetylene, 1a

To a solution of 516 mg (3.20 mmol) of hexamethyldisilazane in 10 ml of diethyl ether, cooled to 0°C, were added *via* syringe n-BuLi (2.0 ml, 1.6 M in hexanes, 3.20 mmol). After 5 minutes the system was cooled to −78°C and 131 mg (1.0 mmol) of trichloroethylene in 5 ml of diethyl ether

were added. The temperature was raised slowly to 0°C, and 340 mg (2.0 mmol) of (1*S*,2*S*,4*S*)-1,7,7-trimethylbicyclo-[2.2.1]heptane-2-thiol **2a** dissolved in 6 ml of diethyl ether were added. The mixture was then allowed to warm up to room temperature and stirred for 24 h. After this time, the mixture was poured over hexane, and water was added cautiously. Phases were separated, and the organic one was washed twice with 20 ml of a 1M NaOH solution. The combined organic extracts were dried and the solvents removed *in vacuo*. The residual oil was purified by chromatography to give 338 mg (93%) of **1a** as an oil that crystallised on standing at −18°C. Colourless crystals, m.p. 145°C. $[\alpha]_D^{23}$=+87.1 (*c* 1.06 $CHCl_3$). IR (film) 3000–2900, 1450, 1390, 1275 cm^{-1}. ^{1}H-NMR δ=0.83 (s, 6H), 0.91 (s, 6H), 1.05 (s, 6H), 0.8–1.3 (m, 6H), 1.5–2.0 (m, 8H), 3.1 (dd, 2H). ^{13}C-NMR δ=13.3 ($2CH_3$), 20.1 ($2CH_3$), 20.2 ($2CH_3$), 27.2 ($2CH_2$), 38.0 ($2CH_2$), 38.2 ($2CH_2$), 45.7 (2CH), 47.4 (2Cq), 49.5 (2Cq), 59.7 (2CH), 87.6 (2Cq). MS (CI-NH_3) m/e=397 (M^++35, 3%), 380 (M^++18, 65%), 363 (M^++1, 100%). Elemental analysis: Calculated for $C_{22}H_{34}S_2$: C 72.87%, H 9.45%, S 17.68%; found: C 73.04%, H 9.54%, S 17.59%.

Preparation of 1,2-bis[(1S,2R,3S,4R)-3-(2,2-dimethylpropoxy)-4,7,7-trimethylbicyclo[2.2.1]heptyl-2-thio]acetylene, ***1b***

The above procedure was followed starting from 516 mg (3.20 mmol) of hexamethyldisilazane, 2.0 ml (1.6 M in hexanes, 3.20 mmol) of n-BuLi, 131 mg (1.0 mmol) of trichloroethylene and 512 mg (2.0 mmol) of (1*S*,2*R*,3*S*,4*R*)-3-(2,2-dimethylpropoxy)-4,7,7-trimethylbicyclo[2.2.1]heptane-2-thiol **2b**. The reaction took 48 h to completion. After the purification, 523 mg (98%) of **1b** were obtained as a white solid, m.p. 143°C. $[\alpha]_D^{23}$=−120.6 (c 1.10 $CHCl_3$). IR (KBr) 2960, 2880, 1475, 1390, 1120, 1105, 1080 cm^{-1}. ^{1}H-NMR δ=0.79 (s, 6H), 0.89 (s, 6H), 0.91 (s, 18H), 1.17 (s, 6H), 0.8–1.9 (m, 8H), 2.0 (d, 2H), 3.00 (d, J=7.6 Hz, 2H), 3.38 (d, J=7.6 Hz, 2H), 3.28, 3.44 (AB, J=7.6 Hz, 4H). ^{13}C-NMR δ=11.9 ($2CH_3$), 21.1 ($2CH_3$), 21.4 ($2CH_3$), 26.9 ($2CH_3$), 28.3 ($2CH_2$), 32.8 (2Cq), 33.3 ($2CH_2$), 47.0 (2Cq), 50.8 (2Cq), 51.1 (2CH), 61.2 (2CH), 83.9 ($2CH_2$), 87.2 (2Cq), 88.1 (2CH). MS (CI-NH_3) m/e=535 (M^++1, 100%). Elemental analysis: Calculated for $C_{32}H_{54}O_2S_2$: C 71.86%, H 10.18%, S 11.99%; found: C 71.96%, H 10.38%, S 11.92%.

Quenching of the reaction after 24 h yielded after the usual treatment and purification 235 mg (48%) of the acetylene dithioether **1b** and 114 mg (20%) of 1-[(1*S*,2*R*,3*S*,4*R*)-3-(2,2-dimethylpropoxy)-4,7,7-trimethylbicyclo[2.2.1]heptyl-2-thio]-2-chloroacetylene **3b** as a colourless oil. IR (film) 2960, 2870, 2150, 1470, 1455, 1390, 1360, 1120, 1105, 1080 cm^{-1}. ^{1}H-NMR δ=0.80 (s, 3H), 0.90 (s, 9H), 0.91 (s, 3H), 1.17 (s, 3H), 0.9–1.9 (m, 4H), 2.0 (d, 1H), 3.04 (d, J=7.2 Hz, 1H), 3.31 (d, 1H), 3.35 (d, 1H), 3.46 (d, 1H). ^{13}C-NMR δ=11.83 (CH_3), 21.0 (CH_3), 21.4 (CH_3), 26.8 ($3CH_3$), 28.3 (CH_2), 32.7 (Cq), 33.1 (CH_2), 47.1 (Cq), 50.8 (Cq), 51.0 (CH), 59.7 (CH), 62.3 (Cq), 84.0 (CH_2), 88. (CH), acetylenic Cq not observed. MS (CI-NH_3) m/e=334 (12%), 332 (32%), 317 (10%), 315 (24%), 231 (36%), 229 (100%).

Preparation of 1,2-bis[(1R,2R,4R)-7,7-dimethyl-1-methylsulfanyl-methylbicyclo[2.2.1]heptyl-2-thio]acetylene, ***1c***

The general procedure was followed starting from 259 mg (1.60 mmol) of hexamethyldisilazane, 1.0 ml (1.6 M in hexanes, 1.60 mmol) of n-BuLi, 66 mg (0.5 mmol) of trichloroethylene and 216 mg (1.0 mmol) of (1*R*,2*R*,4*R*)-7,7-dimethyl-1-methylsulfanylmethylbicyclo[2.2.1]heptane-2-thiol **2c**. The reaction took 48 h to completion. After the purification 216 mg (96%) of **1c** were obtained as a colourless oil. $[\alpha]_D^{23}$=−73.7 (c 0.91 $CHCl_3$). IR (film)=3000–2900, 1460, 1390, 1310, 1255, 960 cm^{-1}. ^{1}H-NMR δ=0.88 (s, 6H), 0.96 (s, 6H), 1.0–2.2 (m, 14H), 2.16 (s, 6H), 2.60, 2.80 (AB, J=12.0 Hz, 4H), 3.36 (dd, 2H). ^{13}C-NMR δ=17.7 ($2CH_3$), 20.2 ($2CH_3$), 20.6 ($2CH_3$), 27.0 ($2CH_2$), 34.7 ($2CH_2$), 35.4 ($2CH_2$), 38.3 ($2CH_2$), 46.1 (2CH), 48.3 (2Cq), 53.3 (2Cq), 57.0 (2CH), 87.7 (2Cq). MS (CI-NH_3) m/e=472 (M^++18, 4%), 455 (M^++1, 100%).

Preparation of 1,2-bis[(1R,2R,4R)-7,7-dimethyl-1-mesitylsulfanylmethylbicyclo[2.2.1]heptyl-2-thio]acetylene, ***1d***

The general procedure was followed using 129 mg (0.80 mmol) of hexamethyldisilazane, 0.5 ml (1.6 M in hexanes, 0.8 mmol) of n-BuLi, 33 mg (0.25 mmol) of trichloroethylene and 167 mg (0.5 mmol) of (1*R*,2*R*,4*R*)-7,7-dimethyl-1-mesitylsulfanylmethylbicyclo[2.2.1]heptane-2-thiol **2d**. The reaction is complete after 24 h. After the purification 172 mg (100%) of **1d** were obtained as a colourless oil. $[\alpha]_D^{23}=-62.0$ (c 1.12 $CHCl_3$). IR (film)=3000–2900, 1460, 1400, 1380, 1315, 1255, 910, 855 cm^{-1}. ^{1}H-NMR δ=0.85 (s, 6H), 0.95 (s, 6H), 1.0–2.2 (m, 14H), 2.22 (s, 6H), 2.40 (s, 12H), 2.64, 2.85 (AB, J=12.4 Hz, 4H), 3.30 (dd, 2H), 3.78 (AB, J=3 Hz, 4H), 6.80 (s, 4H). ^{13}C-NMR δ=19.7 ($4CH_3$), 20.3 ($2CH_3$), 20.6 ($2CH_3$), 20.8 (2 CH_3), 27.0 ($2CH_2$), 33.0 ($2CH_2$), 33.6 ($2CH_2$), 34.4 ($2CH_2$), 38.4 ($2CH_2$), 46.3 (2CH), 48.4 (2Cq), 53.3 (2Cq), 56.9 (2CH), 87.8 (2Cq), 128.8 (4CH), 131.2 (2Cq), 136.2 (2Cq), 136.9 (4Cq). MS (CI-NH_3) m/e=708 (M^++1, 100%).

Pauson–Khand reaction of ***1b*** *with norbornadiene*

a) Thermal activation

To a solution of 36 mg (0.103 mmol) of $Co_2(CO)_8$ in 2 ml of isooctane were added 50 mg (0.094 mmol) of **1b** dissolved in 3 ml of isooctane. After 5 minutes, 86 mg (0.94 mmol) of norbornadiene were added to the mixture, and the temperature was raised to 90°C. After 2 h, the mixture was cooled to room temperature, filtered over Celite 545, the solvent evaporated *in vacuo*, and the residue purified by column chromatography using hexane/diethyl ether mixtures as eluent, to obtain 14 mg (23%) of the adduct **4**. HPLC (Nucleosil 120 C18 (20 cm), CH_3OH:H_2O 90:10 to 100:0 in 120 minutes, 0.8 ml/min): 58.5 min (19.8%), 60.1 min (80.1%).

b) N*-Oxide promoted*

To a solution of 36 mg (0.103 mmol) of $Co_2(CO)_8$ in 2 ml of CH_2Cl_2 were added 50 mg (0.094 mmol) of **1b** dissolved in 3 ml of CH_2Cl_2. After 5 minutes, 86 mg (0.94 mmol) of norbornadiene were added. The mixture was cooled to −20°C and 66 mg (0.56 mmol) of *N*-methylmorpholine-*N*-oxide were added. After the addition, the cooling bath was replaced for an ice bath, and the temperature kept to 0°C overnight. After 15 h, the mixture was filtered over Celite 545, the solvent evaporated *in vacuo*, and the residue purified by column chromatography using hexane/diethyl ether mixtures as eluent, to obtain 15 mg (25%) of the adduct **4**. HPLC (Nucleosil 120 C18 (20 cm), CH_3OH:H_2O 90:10 to 100:0 in 120 minutes, 0.8 ml/min): 58.5 min (14%), 60.1 min (86%). IR (film) 2945, 2860, 1675, 1495, 1465, 1450, 1380, 1350, 1225, 1110, 1100, 1070, 705 cm^{-1}. ^{1}H-NMR d=0.75 (s, 3H), 0.84 (s, 3H), 0.89 (s, 9H), 0.92 (s, 9H), 0.94 (s, 3H), 0.96 (s, 3H), 1.20 (s, 3H), 1.25 (s, 3H), 0.9–2.0 (m, 14H), 2.44 (d, 1H), 2.8–4.0 (m, 9H), 6.25 (b, 2H). ^{13}C-NMR δ=12.0 (CH_3), 12.1 (CH_3), 20.9 (CH_3), 21.2 (CH_3), 21.4 ($2CH_3$), 26.94 ($3CH_3$), 26.99 ($3CH_3$), 28.0 (CH_2), 28.7 (CH_2), 32.6 (Cq), 32.7 (Cq), 33.3 (CH_2), 33.4 (CH_2), 41.5 (CH_2), 44.0 (CH), 44.7 (CH), 47.2 (CH), 47.3 (CH), 47.4 (2Cq), 50.4 (Cq), 50.5 (Cq), 50.6 (CH), 50.8 (CH), 53.9 (CH), 54.4 (CH), 83.6 (CH_2), 83.7 (CH_2), 89.0 (CH), 89.2 (CH), 137.1 (CH), 137.9 (CH), 138.1 (Cq), 179.9 (Cq), 202.1 (Cq). MS (CI-NH_3) m/e=624 (1%), 586 (1%), 289 (12%), 229 (39%), 212 (100%).

Acknowledgements

Financial support from CIRIT-CICYT (QFN93-4407), from DGICYT (PB95-0265) and from CIRIT (GRQ93-1083) is gratefully acknowledged. Jaume Balsells thanks CIRIT for a fellowship.

References

1. (a) Riera, A.; Martí, M.; Moyano, A.; Pericàs, M. A.; Santamaría, J. *Tetrahedron Lett.* **1990**, *31*, 2173–2176. (b) Belloc, J.; Virgili, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 4579–4582. (c) Virgili, M.; Belloc, J.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron*

Lett. **1991**, *32*, 4583–4586. (d) Hickey, E. R.; Paquette, L. A. *J. Am. Chem. Soc.* **1995**, *117*, 163–176. (e) Gleiter, R.; Ohlbach, F.; Oeser, T.; Irngartinger, H. *Liebigs Ann.* **1996**, 785–790.
2. (a) Fischer, H.; Treier, K.; Troll, C. *Chem. Ber.* **1995**, *128*, 1149–1156. (b) Fischer, H.; Treier, K.; Troll, C.; Stumpf, R. *J.C.S., Chem. Commun.* **1995**, 2461–2463.
3. Riera, A.; Cabré, F.; Moyano, A.; Pericàs, M. A.; Santamaría, J. *Tetrahedron Lett.* **1990**, *31*, 2169–2172.
4. Montenegro, E.; Echarri, R.; Claver, C.; Castillón, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron: Asymmetry*, **1996**, *7*, 3553–3558.
5. Several lots of potassium hydride (35 wt. % dispersion in mineral oil, Aldrich 21,581-3 and pract.; under oil, Fluka 60328) have been tested in the reaction with erratic results. This behaviour should be taken into account when preparing solutions of dichloroacetylene in THF by the method of Greene.[6]
6. Denis, J.N.; Moyano, A.; Greene, A.E. *J. Org. Chem.* **1987**, *52*, 3461–3462
7. Kende, A.S.; Fludzinski, P. *Synthesis* **1982**, 455–456.
8. Blanco, J.M.; Caamaño, O.; Eirín, A.; Fernández, F.; Medina, L. *Synthesis* **1990**, 584–586.
9. Lee, D.-S.; Hung, S.-M.; Lai, M.-C.; Chu, H.-Y.; Yang, T.-K. *Org. Prep. Proc. Int.* **1993**, *25*, 673–679.
10. Panov, D.; Marchueta, I.; Moyano, A.; Pericás, M. A.; Riera, A. Unpublished results.
11. For a recent review, see: Schore, N. E., in *Comprehensive Organometallic Chemistry*; Hegedus, L. S. Ed.; Elsevier: Oxford 1995; vol. 12, pp. 703–739.
12. For previous work on diastereoselective intermolecular Pauson–Khand reactions based on the use of chiral auxiliaries, see: (a) Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A.; Bernardes, V.; Greene, A. E.; Alvarez-Larena, A.; Piniella, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 2153–2154, (b) Bernardes, V.; Verdaguer, X.; Kardos, N.; Riera, A.; Moyano, A.; Pericàs, M. A.; Greene, A. E. *Tetrahedron Lett.* **1994**, *35*, 575–578. (c) Fonquerna, S.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron* **1995**, *51*, 4239–4254.
13. Montenegro, E., Ph.D. Thesis, Universitat de Barcelona, 1995.

(Received in UK 4 March 1997)