Pergamon

PII: S0031-9422(97)01032-7

Phytochemistry, Vol. 48, No. 4, pp. 687–691, 1998

Printed in Great Britain
0031-9422/98 $19.00+0.00

NEO-CLERODANE DITERPENOIDS FROM *SCUTELLARIA LATERIFLORA*

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(*Received* 17 *October* 1997)

Key Word Index—*Scutellaria lateriflora*; Labiatae; neo-clerodane diterpenes; scutelaterins A–C; ajugapitin; scutecyprol A.

Abstract—Three new diterpenoids, scutelaterins A–C, have been isolated from *Scutellaria lateriflora* and their structures established as (11*S*,13*S*,16*S*)-2β,6α,19-triacetoxy-4α,18;11,16;15,16-triepoxy-neo-clerod-14-ene (scutelaterin A), (11*S*,13*S*,16*S*)-6α,19-diacetoxy-2β-(2′-methyl)butyryloxy-4α,18;11,16;15,16-triepoxy-neo-clerod-14-ene (scutelaterin B) and (11*S*,13*S*,15*R* and *S*)-6α,19-diacetoxy-2β-(2′-methyl)butyryloxy-4α,18;11,16;15,16-triepoxy-neo-clerodan-15-ol (scutelaterin C) by chemical and spectroscopic means. In addition, the already known neo-clerodanes ajugapitin and scutecyprol A were also found in the same source.

INTRODUCTION

In continuation of our systematic studies of neo-clerodane diterpenoids within the genus *Scutellaria* [1–4], we have investigated the aerial parts of *S. lateriflora*. We report here on the isolation and structure determination of three new diterpenes (scutelaterins A–C) as well as the identification of the already known neo-clerodanes ajugapitin and scutecyprol A.

RESULTS AND DISCUSSION

An acetone extract of the aerial parts of *S. lateriflora* was subjected to extensive chromatography (see Experimental) to yield the already known neo-clerodane diterpenoids ajugapitin (**1**) [5] and scutecyprol A (**2**) [6, 7], the latter as a mixture of the C-15 epimers, the 15*R* form of which was previously known as clerodin hemiacetal [7, 8]. In addition, three new neo-clerodanes, scutelaterins A–C (**3–5**, respectively) were also isolated from the same plant and their structures established as follows.

Scutelaterin A (**3**) was assigned the molecular formula $C_{26}H_{36}O_9$ and its IR spectrum showed absorptions for vinyl ether (3100, 1615 cm^{-1}) and ester (1730, 1240 cm^{-1}) groups and was devoid of hydroxyl absorptions. The ^1H and ^{13}C NMR spectra of **3** (Tables 1 and 2, respectively) revealed the presence of three acetoxyl groups and characteristic signals of a neo-clerodane diterpene [δ_H 0.84 *d*, 3H, J = 6.3 Hz (Me-17) and 0.96 *s*, 3H (Me-20); δ_C 16.4 *q* (C-17) and 13.9 *q* (C-20)] having a 4α,18-oxirane [δ_H 2.29 *d*, 1H, J_{gem} = 3.9 Hz (H_A-18) and 3.10 *dd*, 1H, J_{gem} = 3.9 Hz, $J_{18B,3\alpha}$ = 2.1 Hz (H_B-18); δ_C 61.4 *s* (C-4) and 49.7 *t* (C-18)], an esterified 6α-hydroxyl group ($\delta_{H\text{-}6\beta}$ 4.74 *dd*, $J_{6\beta,7\alpha}$ = 11.3 Hz, $J_{6\beta,7\beta}$ = 4.5 Hz; $\delta_{C\text{-}6}$ 72.1 *d*), a C-19 acyloxy grouping (δ_H 4.36 *d* and 4.85 *d*, J_{gem} = 12.5 Hz; $\delta_{C\text{-}19}$ 61.7 *t*) and a tetrahydrofurofuran moiety involving C-11–C-16 carbons. The presence of a C-14, C-15 olefinic double bond in this structural part was revealed by the ^1H NMR signals at δ 4.79 (1H, *t*, $J_{14,13} = J_{14,15}$ = 2.5 Hz, H-14) and 6.44 (1H, *t*, $J_{15,13} = J_{15,14}$ = 2.5 Hz), and the carbon atom resonances at δ 101.8 *d* (C-14) and 146.9 *d* (C-15). All these functionalities have been found in several neo-clerodane derivatives previously isolated from *Scutellaria* species [1–8].

In addition, scutelaterin A (**3**) possessed the third acetoxyl group attached to the C-2β axial position of the neo-clerodane nucleus (δ_C 70.6 *d*, geminal proton as a *quintuplet* at δ 5.16, J = 2.9 Hz), as was revealed by the small coupling values of its geminal proton with the C-1 and C-3 methylene protons (Table 1). This was also in agreement with double resonance experiments, because irradiation at δ 5.16 (H-2α)

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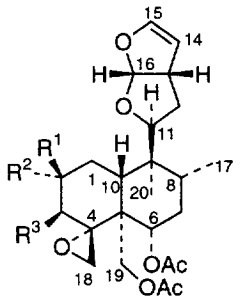
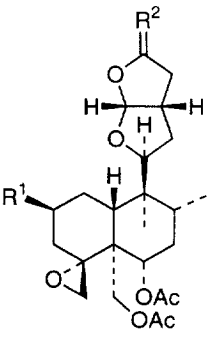
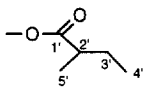




	R^1	R^2	R^3
1	H	OH	
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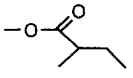
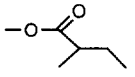
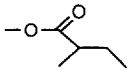
4		H	H

	R^1	R^2
2	H	H,OH (*)
5		H,OH (*)
6		O

*, Mixture of 15*R* and 15*S* forms.

transformed the signal of the H-3α axial proton (δ 2.38 *dd*, $J_{3\alpha,3\beta}$ = 14.6 Hz, $J_{3\alpha,2\alpha}$ = 2.9 Hz, $J_{3\alpha,18B}$ = 2.1 Hz) into a double doublet ($J_{3\alpha,3\beta}$ = 14.6 Hz, $J_{3\alpha,18B}$ = 2.1 Hz) and the signal of the H-1β equatorial proton (δ 2.45 *ddd*, $J_{1\beta,1\alpha}$ = 15.6 Hz, $J_{1\beta,2\alpha}$ = 2.8 Hz, $J_{1\beta,10\beta}$ = 2.9 Hz) into another double doublet (*J* = 15.6 and 2.9 Hz). Comparison of the ^{13}C NMR spectrum of **3** (Table 2) with those of other 2-acetoxy-neo-clerodane derivatives [4, 9, 10] further supported the presence of a 2β-acetoxyl group in scutelaterin A (**3**).

Scutelaterin B (**4**, $C_{29}H_{42}O_9$) gave ^{1}H and ^{13}C NMR spectra almost identical with those of scutelaterin A (**3**, $C_{26}H_{36}O_9$, see Tables 1 and 2) and the observed differences were consistent with the presence in **4** of a 2-methylbutanoyloxy substituent [δ_H 2.32 *sext*, 1H, *J* = 7.1 Hz (H-2′), 0.91 *t*, 3H, *J* = 7.4 Hz (Me-4′) and 1.13 *d*, 3H, *J* = 7.1 Hz (Me-5′); δ_C 175.3 *s* (C-1′), 41.4 *d* (C-2′), 26.7 *t* (C-3′), 11.7 *q* (C-4′) and 16.6 *q* (C-5′)] [1] instead of one of the acetoxyl groups of **3**. The HMBC spectrum of **4** showed correlations through three bonds between the carboxyl carbon belonging to the 2-methylbutanoate (δ 175.3 *s*) and the H-2α proton (δ 5.19 *quint*, *J* = 2.9 Hz), whereas the carboxyl carbons of the acetates at δ 170.6 *s* and 170.1 *s* correlated with the C-19 methylene (δ 4.36 *d* and 4.85 *d*, J_{gem} = 12.4 Hz) and the C-6β methine (δ 4.73 *dd*, *J* = 11.7 and 4.6 Hz) protons, respectively. These results firmly supported structure **4** for this new diterpenoid.

Scutelaterin C (**5**) was homogeneous on TLC and its ^{1}H and ^{13}C NMR spectra (see Experimental) showed essentially the same signals as those present in the spectra of **4** (Tables 1 and 2). The observed differences between the NMR spectra of **5** and **4** were in agreement with the former being a mixture of the C-15 epimers of the 14,15-dihydro-15-hydroxy derivative of **4** [1, 4, 6, 7]. Treatment of **5** with an excess of Jones' reagent gave the lactone **6** ($C_{29}H_{42}O_{10}$, see Tables 1 and 2 and Experimental) by oxidation of the C-15 hemiacetal [1, 4, 6, 7], whereas treatment of **4** with the same reagent also yielded **6**, but in this case by an initial addition of water to the 14,15-vinyl ether [1, 4, 7, 8] followed by oxidation of the resulting C-15 hemiacetal. This correlation supported structure **5** for scutelaterin C.

The absolute configuration of compounds **3**–**6** was not ascertained. However, we assume that, on biogenetic grounds, these compounds belong to the neoclerodane [11] class, like other diterpenes isolated from *Scutellaria* species [2, 3, 4, 7]. In addition, for the above reasons, the absolute stereochemistry at the C-2 stereogenic centre of the 2-methylbutyrate part of **4**, **5** and **6** is probably 2*S* [12, 13].

EXPERIMENTAL

General

Mps uncorr. *Scutellaria lateriflora* L. was cultivated in the 'Orto Botanico dell'Università di Milano' at Tuscolano (Brescia, Italy). Seeds of the species were provided by the 'Jardin Botanique de Montréal',

Table 1. ^{1}H NMR spectral data for compounds **3**, **4** and **6** [$CDCl_3$, δ values relative to residual $CHCl_3$ (δ 7.25)]*

H	3†	4‡	6§	*J* (Hz)	3†	4‡	6§
1α	¶	1.87 *ddd*	¶	1α,1β	15.6	15.7	¶
1β	2.45 *ddd*	2.43 *ddd*	¶	1α,2α	2.9	2.9	2.8
2α	5.16 *quint*	5.19 *quint*	5.14 *quint*	1α,10β	13.0	13.2	¶
3α	2.38 *ddd*	2.39 *ddd*	¶	1β,2α	2.9	2.9	2.8
3β	¶	1.29 *dd*	¶	1β,10β	2.8	2.8	¶
6β	4.74 *dd*	4.73 *dd*	4.70 *dd*	2α,3α	2.9	2.9	2.8
7α	¶	~1.65¶	¶	2α,3β	2.9	2.9	2.8
7β	¶	~1.46¶	¶	3α,3β	14.6	14.5	¶
8β	¶	~1.46¶	¶	3α,18B‡‡	2.1	2.1	2.1
10β	2.09 *dd*	2.09 *dd*	¶	6β,7α	11.3	11.7	11.3
11α	4.01 *dd*	4.01 *dd*	4.09 *dd*	6β,7β	4.5	4.6	4.8
12A	¶	~1.65¶	¶	6β,19A	0	0	~0.5
12B	¶	1.76 *ddd*	¶	8β,17	6.3	6.6	6.3
13β	3.49 *m*#	3.44 *m*#	3.04 *m***	11α,12A	4.9	4.5	5.3
14A	4.79 *t*	4.78 *t*	~2.35¶	11α,12A	11.3	11.8	11.7
14B	—	—	2.84 *dd*	12A,12B	¶	11.8	¶
15	6.44 *t*	6.43 *t*	—	12B,13β	¶	8.1	¶
16β	5.98 *d*	5.95 *d*	5.97 *d*	13β,14	2.5	2.7	¶
Me-17	0.84 *d*	0.83 *d*	0.84 *d*	13β,15	2.5	2.4	—
18A††	2.29 *d*	2.27 *d*	2.25 *d*	13β,14B	—	—	10.5
18B‡‡	3.10 *dd*	3.08 *dd*	3.05 *dd*	13β,16β	6.2	6.1	5.5
19A	4.36 *d*	4.36 *d*	4.35 *br d*	14A, 14B	—	—	18.4
19B	4.85 *d*	4.85 *d*	4.81 *d*	14,15	2.5	2.7	—
Me-20	0.96 *s*	0.97 *s*	0.94 *s*	18A,18B	3.9	3.9	4.1
2β-OAc	2.03 *s*	—	—	19A,19B	12.5	12.4	12.5
6α-OAc	1.95 *s*	1.94 *s*	1.92 *s*	2′,3′A	—	7.1	¶
19-OAc	2.09 *s*	2.08 *s*	2.06 *s*	2′,3′B	—	7.1	¶
2′	—	2.32 *sext*	~2.30¶	2′,5′	—	7.1	7.0
3′A	—	~1.46¶	¶	3′A,3′B	—	¶	¶
3′B	—	~1.65¶	¶	3′A,4′	—	7.4	7.4
Me-4′	—	0.91 *t*	0.89 *t*	3′B,4′	—	7.4	7.4
Me-5′	—	1.13 *d*	1.10 *d*				

* Spectral parameters were obtained by first-order approximation.
† At 300 MHz.
‡ At 500 MHz.
§ At 200 MHz.
¶ Overlapped signal. In the case of **4**, approximate δ values for overlapped protons were assigned from the HMQC spectrum.
# $W_{1/2}$ = 16 Hz.
** $W_{1/2}$ = 20 Hz.
†† *Exo* hydrogen with respect to ring B.
‡‡ *Endo* hydrogen with respect to ring B.

Montreal, Canada. Plant materials were collected in July 1996 and voucher specimens have been deposited in the Herbarium of the Dipartimento di Biologia, University of Milan, Italy.

Extraction and isolation of the diterpenoids

Air-dried and powdered aerial parts of *S. lateriflora* L. (3.75 kg) were extracted with Me_2CO (3 × 10 l) at room temp. for one week. The extract (151 g) was subjected to CC (silica gel, Merck No. 7734, deactivated with 10% H_2O, w/v, 800 g) eluting with a petrol–EtOAc gradient. The frs eluted with petrol–EtOAc (7:3) were rechromatographed [CC, silica gel, CH_2Cl_2–petrol (9:1) as eluent] yielding scutelaterin C (**5**, 25 mg). The fractions eluted with petrol–EtOAc (3:2) gave, after radial chromatography [silica gel disk, CH_2Cl_2-MeOH (24:1) as eluent], scutelaterin B (**4**, 80 mg). Radial chromatography (as above) of the fractions eluted with EtOAc–petrol (1:1) successively yielded scutelaterin A (**3**, 20 mg) and ajugapitin (**1**, 200 mg). Finally, the fractions eluted with EtOAc–petrol (4:1) were rechromatographed [CC, silica gel, CH_2Cl_2-petrol (9:1) as eluent] giving scutecyprol A (**2**, 50 mg). All chromatographic fractions containing the diterpenes were decolourized by filtration through a pad of a mixt. (1:1) of activated charcoal and celite, eluting with EtOAc.

Table 2. ^{13}C NMR spectral data for compounds **3**, **4** and **6***

C	3	4	6	C	3	4	6
1	26.9 *t*	27.3 *t*	27.2 *t*	16	107.6 *d*	107.6 *d*	106.4 *d*
2	70.6 *d*	70.2 *d*	70.3 *d*	17	16.4 *q*	16.2 *q*	16.2 *q*
3	36.7 *t*	36.9 *t*	36.8 *t*	18	49.7 *t*	49.7 *t*	49.6 *t*
4	61.4 *s*	61.4 *s*	61.3 *s*	19	61.7 *t*	61.8 *t*	61.7 *t*
5	45.1 *s*	45.1 *s*	45.0 *s*	20	13.9 *q*	13.9 *q*	13.7 *q*
6	72.1 *d*	72.2 *d*	71.9 *d*	OAc	170.7 *s*	170.6 *s*†	170.4 *s*
7	33.3 *t*	33.3 *t*	33.2 *t*		170.1 *s*	170.1 *s*‡	169.9 *s*
8	36.2 *d*	36.4 *d*	36.2 *d*		170.0 *s*	21.2 *q*	21.0 *q*
9	39.6 *s*	39.7 *s*	39.9 *s*		21.0 *q*	21.1 *q*	21.0 *q*
10	42.2 *d*	42.5 *d*	42.0 *d*		21.0 *q*	—	—
11	84.4 *d*	84.6 *d*	84.3 *d*		21.0 *q*	—	—
12	30.9 *t*	30.8 *t*	31.9 *t*	1′	—	175.3 *s*	175.3 *s*
13	46.1 *d*	46.1 *d*	37.9 *d*	2′	—	41.4 *d*	41.3 *d*
14	101.8 *d*	101.8 *d*	35.0 *t*	3′	—	26.7 *t*	26.6 *t*
15	146.9 *d*	146.9 *d*	174.8 *s*	4′	—	11.7 *q*	11.6 *q*
				5′	—	16.6 *q*	16.5 *q*

*Spectra were obtained at 50 MHz, except for **4** (125 MHz), in $CDCl_3$ solution. Chemical shifts are reported in δ values and are relative to the solvent signals (δ_{CDCl_3} 77.00). Multiplicities were determined by the DEPT (135°) pulse sequence and, in the case of **4**, by the HMQC spectrum. All the assignments for **4** were in agreement with the HMBC and HMQC spectra.

† Acetate at C-19, assigned from the HMBC spectrum.

‡ Acetate at C-6, assigned from the HMBC spectrum.

The previously known compounds, ajugapitin (**1**) [5] and scutecyprol A (**2**) [6, 7], were identified by their physical (mp, $[\alpha]_D$) and spectroscopic (^1H NMR, IR and MS) data and, in the case of **1**, by comparison (mmp, TLC) with an authentic sample.

Scutelaterin A (**3**). Amorphous solid, mp 50–60°; $[\alpha]_D^{21}$ +1.2° ($CHCl_3$; *c* 0.064). IR ν_{max}^{KBr} cm^{-1}: 3100, 1615 (vinyl ether), 1730 *br*, 1240 *br* (OAc), 2960, 1440, 1370, 1085, 1020, 860; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EI-MS (70 eV, direct inlet) *m/z* (rel. int.): 492 $[M]^+$ (1), 432 $[M\text{-}AcOH]^+$ (0.7), 317 (1), 287 (1), 263 (1), 213 (2), 203 (4), 201 (8), 189 (6), 185 (6), 173 (9), 171 (17), 157 (8), 145 (6), 111 [side chain at C-9]$^+$ (20), 105 (9), 91 (12), 83 (10), 81 (11), 69 (9), 55 (13), 43 (100), 41 (7). (Found: C, 63.16; H, 7.41. $C_{26}H_{36}O_9$ requires: C, 63.40; H, 7.37%).

Scutelaterin B (**4**). Mp 118–120° (EtOAc–*n*-hexane); $[\alpha]_D^{26}$ −4.2° ($CHCl_3$; *c* 0.311). IR ν_{max}^{KBr} cm^{-1}: 3100, 1620 (vinyl ether), 1730 *br*, 1250 *br* (esters), 2980, 2940, 2880, 1465, 1380, 1190, 1150, 1090, 1025, 1000, 950, 865, 720; ^1H NMR: Table 1; ^{13}C NMR: Table 2; EI-MS (70 eV, direct inlet) *m/z* (rel. int.): 534 $[M]^+$ (5), 432 $[M\text{-}C_5H_{10}O_2]^+$ (4), 390 (4), 317 (4), 287 (4), 202 (17), 201 (18), 189 (12), 185 (13), 173 (20), 171 (33), 169 (10), 159 (13), 157 (13), 145 (11), 143 (11), 111 [side chain at C-9]$^+$ (37), 107 (13), 105 (11), 95 (12), 91 (17), 83 (25), 81 (28), 69 (34), 57 (100), no ion fragments below *m/z* 55 were registered. (Found: C, 65.21; H, 7.78, $C_{29}H_{42}O_9$ requires: C, 65.15; H, 7.92%).

Scutelaterin C (**5**). Thick oil; mixture 1:1.3 of the 15*R* (*exo*) and 15*S* (*endo*) forms, respectively; ^1H NMR (300 MHz, $CDCl_3$): δ 5.79 *d*, 0.4 H, and 5.75 *d*, 0.6 H, J = 5.5 Hz (H-16β), 5.66 *br d*, 0.4 H, and 5.54 *d*, 0.6 H, J = 5.5 Hz (H-15), 5.23 *quint*, 0.4 H, and 5.18 *quint*, 0.6 H, J = 2.8 Hz (H-2α), 4.90 *d*, 1H, J = 12.4 Hz (H_B-19), 4.77 *dd*, 1H, J = 10.8 and 4.9 Hz (H-6β), 4.56 *dd*, 0.6 H, and 4.02 *dd*, 0.4 H, J = 11.3 and 5.4 Hz (H-11α), 4.40 *br d*, 1H, J = 12.4 Hz (H_A-19), 3.14 *br*, 1H (H_B-18), 3.02 *m*, 0.4 H, and 2.78 *m*, 0.6 H (H-13β), 2.36 *d*, 0.6 H, and 2.31 *d*, 0.4 H, J = 4.0 Hz (H_A-18), 2.13 *s*, 3H (OAc), 1.99 *s*, 3H (OAc), 1.19 *d*, 1.8 H, and 1.17 *d*, 1.2 H, J = 7.1 Hz (Me-5′), 0.95-0.90 complex signal, 9H (Me-17, Me-20 and Me-4′). ^{13}C NMR (50 MHz, $CDCl_3$): δ(in double signals the first chemical shift correspond to the major 15*S* epimer) 176.1 and 175.4 (C-1′), 170.7 (OAc), 170.1 (OAc), 109.3 and 107.4 (C-16), 98.4 and 98.7 (C-15), 82.7 and 83.7 (C-11), 72.2 and 72.1 (C-6), 70.6 and 70.2 (C-2), 61.8 and 61.7 (C-19), 61.5 and 61.4 (C-4), 49.8 and 49.6 (C-18), 44.9 and 45.1 (C-5), 42.0 and 42.3 (C-13), 41.4–41.2, complex signal (C-10, C-2′), 40.0–39.7, complex signal (C-9, C-14), 37.0 and 36.9 (C-3), 35.2 and 36.2 (C-8), 33.2 and 32.7 (C-12), 33.6 and 33.2 (C-7), 26.6 (C-1), 26.4 (C-3′), 21.2 (2OAc), 16.9 and 16.7 (C-5′), 16.4 and 16.2 (C-17), 13.8 and 13.9 (C-20), 11.7 and 11.8 (C-4′).

Lactone **6** *from scutelaterins B* (**4**) *and C* (**5**). To a soln of **4** (60 mg) in Me_2CO (10 ml) was added an excess of Jones' reagent at 0° with stirring. After 15 min, the excess of Jones' reagent was destroyed by addition of EtOH and then the reaction mixt. was diluted with H_2O (40 ml). Extraction with EtOAc (4 × 20 ml) and work-up as usual gave an amorphous solid, which was percolated through a silica gel column eluted with EtOAc yielding **6** (56 mg): amorphous solid, mp 85–90°; $[\alpha]_D^{26}$ +13.6° ($CHCl_3$; *c* 0.324). IR ν_{max}^{KBr} cm^{-1}: 1790 (γ-lactone), 1730 *br*, 1250 *br* (esters), 2990, 2950, 2890, 1465, 1380, 1180, 1090,

1030, 1000, 970, 930, 870; ^{1}H NMR: Table 1; ^{13}C NMR: Table 2; EI-MS (70 eV, direct inlet) *m/z* (rel. int.): 551 $[MH]^+$ (0.3), 405 (5), 358 (5), 333 (6), 316 (9), 303 (14), 249 (9), 201 (25), 189 (20), 187 (10), 184 (17), 173 (21), 171 (55), 159 (13), 127 (22), 109 (18), 105 (13), 91 (18), 83 (18), 81 (23), 69 (21), 57 (100), 55 (39), no ion fragments below *m/z* 55 were registered. (Found: C, 63.31; H, 7.46. $C_{29}H_{42}O_{10}$ requires: C, 63.25; H, 7.69%).

Oxidation of **5** (15 mg) in the same way gave a compound (12 mg) which was identical ($[\alpha]_D$, IR, ^{1}H NMR and MS) to the lactone **6** obtained from **4** (see above).

Acknowledgements—The authors thank Prof. R. Martínez Alvarez, Servicio de Espectrometría de Masas de la UCM, Madrid, for the mass spectra. This work was supported by funds from MURST, Italy, DGICYT, Spain (grant PB94-0104 and PB96-0830) the bilateral project CNR-CSIC between ICTPN-CNR (Italy) and Instituto de Química Orgánica (Spain), and the Consejería de Educación y Cultura de la Comunidad de Madrid (grant 06G/001/96).

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