Diversity Oriented Synthesis of Hispanane-like Terpene Derivatives from (*R*)-(+)-Sclareolide

María C. de la Torre,*[a] Isabel García,[b] and Miguel A. Sierra[c]

Dedicated to the memory of our friend Dr. Juan Carlos del Amo, who died as a victim of the terrorist attack in Madrid on March 11th, 2004

Abstract: (*R*)-(+)-Sclareolide **1** has been used as a starting material to develop a diversity oriented methodology to access hispanane **28a**, and hispanane-like derivatives **27b**–**27e**. This methodology is based on the intramolecular Friedel–Crafts acylation of the corresponding 12-desoxylabdanoic-like acids **27**, for the construction of the cycloheptane ring which is characteristic of the hispananes. Acids **27** are obtained from alcohols **20**, available by addition of the lithium or magnesium reagents to amide **12** (followed by Luche reduction), or to aldehyde **21**. This sequence has resulted in the preparation of hispanane framework **27a**. The versatility of this methodology therefore allows a structural diversity oriented synthesis, since it allows the access to a wide variety of hispanane-like derivatives.

Keywords: acylation · hispananes · natural products · terpenoids · total synthesis

Introduction

The last years of the 20th century witnessed an enormous grown of diversity oriented synthesis.[1] Contrary to modern combinatorial chemistry,[2] which is able to produce impressive amounts of new compounds but with the shortcoming of the inability to yield new chemical identities, diversity oriented organic synthesis is—according to Schreiber and Burke[1]—a problem-solving technique for transforming a collection of simple and similar starting materials into a collection of more complex and diverse products. In this regard, natural products are ideal templates for achieving an increasing of structural complexity either by performing designed modifications to incorporate new structural motifs[3] or by joining different natural products in a single structure producing natural product derivatives.[4] The increasing awareness of the key role that small molecules play in the protein–protein interactions[5] leading to the production of drug-like molecules,[6] confers an added value to the new structures.

In this context we reported recently[7] the suitability of (*R*)-(+)-sclareolide **1** as a template to yield the diverse tetra- **2** and pentacyclic **3** terpene derivatives by means of the photochemical cyclization of easily available ketones **4** (Scheme 1). Clearly, by modifying the nature of the moieties attached to the (*R*)-(+)-sclareolide template, the resulting products are nicely set up to access to terpene-like products containing the sclareolide scaffold. In fact, the stereochemistry of the bicyclic decaline of (*R*)-(+)-sclareolide framework **1** contributes the necessary stereocenters, and the lactone ring of sclareolide may be manipulated to access to the key intermediates to produce the final terpene-like products.

Natural hispananes are a scarce group of diterpenes that include exclusively three compounds: hispanonic acid **5** and hispaninic acid **6** isolated from *Ballota hispanica*[8] and methyl verticoate **7** isolated from *Sciadopitys verticillata* (Figure 1).[9] The isolation of these compounds in minute amounts precluded the investigation of their biological prop-

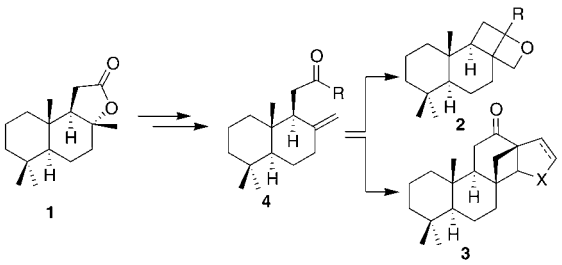
[a] Dr. M. C. de la Torre
Instituto de Química Orgánica
Dpto. de Productos Naturales, CSIC, C/Juan de la Cierva 3
28006 Madrid (Spain)
Fax: (+34) 915-644-853
E-mail: iqot310@iqog.csic.es

[b] Dr. I. García
Present address: Dpto. de Química Orgánica
Facultad de Ciencias, Módulo C-I/Despacho 408
Universidad Autónoma de Madrid, 28049 Madrid (Spain)

[c] Prof. M. A. Sierra
Dpto. de Química Orgánica
Facultad de Química, Universidad Complutense
28040 Madrid (Spain)

Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

 DOI: 10.1002/chem.200401220



Scheme 1. Preparation of polycyclic terpene-like products from (*R*)-(+)-sclareolide.

erties. To date no synthetic approaches to the hispanane skeleton have been reported.

We devised a potentially versatile approach to the hispanane skeleton and hispanane-like derivatives **8** based on a Friedel–Crafts acylation to form the seven-membered ring,

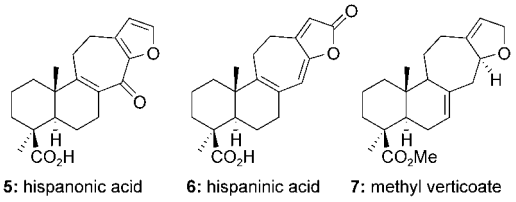
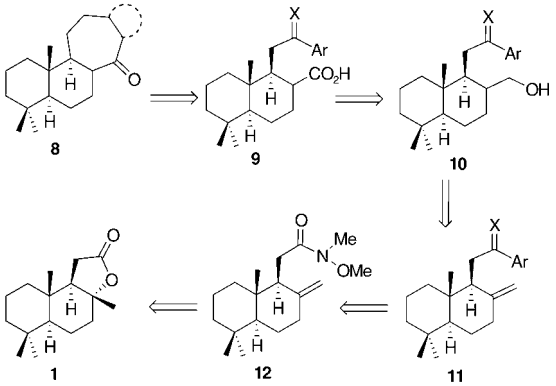


Figure 1. Hispananes isolated from natural sources.

which is characteristic for these types of compounds (Scheme 2). 17-Labdanoic-like acids **9**, the substrates for ring-closure, are prepared by oxidation of the corresponding alcohols **10**, derived from the $\Delta^{8,17}$ unsaturated labdanes **11**; the latter have been already prepared by our group by addition of the appropriate lithium or magnesium reagents to Weinreb amide **12** derived from (*R*)-(+)-sclareolide **1**.[10] Herein we report a versatile and flexible approach to the hispanane skeleton and hispanane-like derivatives **9** starting from (*R*)-(+)-sclareolide **1**.



Scheme 2. Approach to hispanane derivatives **9** from (*R*)-(+)-sclareolide.

Results and Discussion

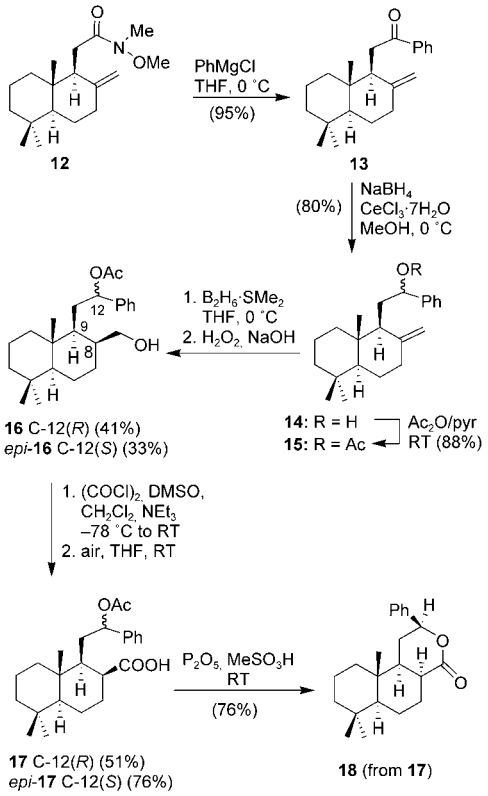
To fine tune the sequence shown in Scheme 2, phenyllabdane ketone **13** was prepared by the reaction of Weinreb's amide **12** and phenylmagnesium bromide in 95% yield. The ketone group of **13** was reduced by using Luche conditions ($NaBH_4/CeCl_3$)[11] to yield the mixture of epimeric alcohols **14**; the alcohols were then acetylated (Ac_2O/py) to form acetates **15**, and treated with $BH_3{\cdot}SMe_2$ followed by oxidative (H_2O_2/NaOH) work-up. The primary alcohols **16** and *epi*-**16** were separated by column chromatography to yield the pure epimers at C-12 (41 and 33% yield, respectively) (Scheme 3).

Alcohols **16** and *epi*-**16** show identical ^1H and ^{13}C data for the decaline moiety and differ only slightly in the side chain at carbon C-9.[12] Therefore we can assume that **16** and *epi*-**16** posses the same stereochemistry at carbon C-8, while they are epimers at carbon C-12. In fact, the presence of an axial-β substituent at carbon C-8 is in accordance with the strong shielding of carbon C-6 in both alcohols **16** ($\delta_{C\text{-}6}$ 18.5) due to a γ-gauche effect, with respect to ketone **13** ($\delta_{C\text{-}6}$ 23.9) having a $\Delta^{8(13)}$ double bond. Equally, the C-20 Me-group in a δ-*syn* axial position with respect to C-8 β-axial substituent appears low-field shifted ($\delta_{C\text{-}20}$ 15.8) with respect to **13** ($\delta_{C\text{-}20}$ 14.8).[13] Regarding to the C-12 stereochemistry of alcohols **16** and *epi*-**16**, the comparison of the H-12 coupling constant values with those for the known compounds (12*R*)- and (12*S*)-15,16-epoxy-12-hydroxylabda-7,13(16),14-trienes evidences that for alcohol **16** ($J = 9.5$ and 4.4 Hz) the values are similar to the (12*R*) series ($J = 10.9$ and 2.7 Hz), while alcohol *epi*-**16** shows values ($J = 8.1$ and 6.5 Hz) related to the (12*S*) series ($J = 8.8$ and 6.6 Hz).[10a] Therefore, it is reasonable to assign a (12*R*) absolute configuration to alcohol **16**, while alcohol *epi*-**16** has (12*S*) absolute configuration.

The oxidation of the C-17 hydroxyl groups of alcohols **16** and *epi*-**16** to the C-12 labdanic acids **17** and *epi*-**17** was ach-

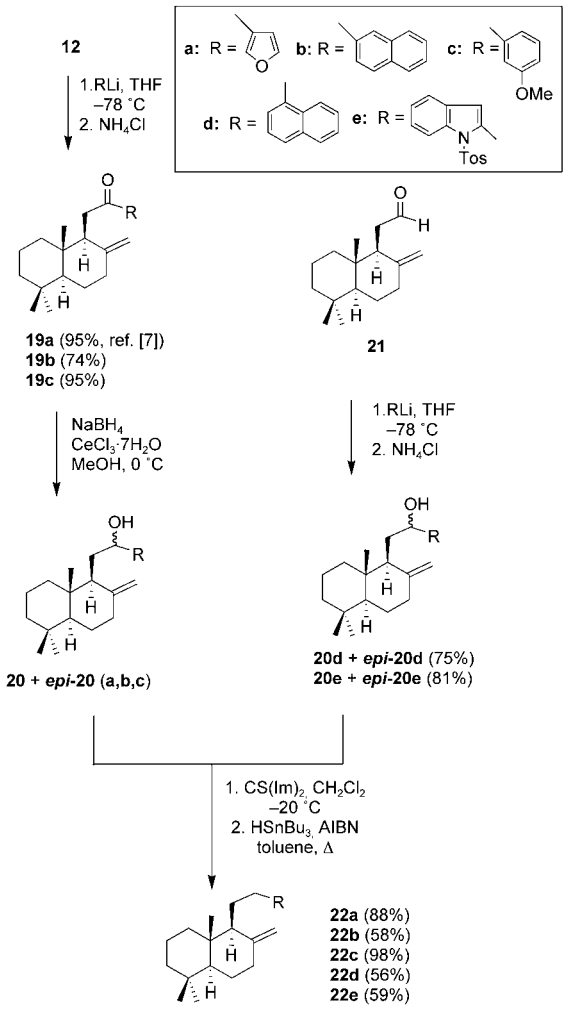
Abstract in Spanish: *El (*R*)-(+)-esclareolido **1** se ha utilizado como material de partida para desarrollar una metodología orientada a obtener diversidad estructural, que ha permitido preparar el hispanano **28a**, y los compuestos de tipo hispanano **28b–28e**. Esta metodología se basa en la acilación intramolecular de tipo Friedel–Crafts de los ácidos 12-desoxilabdanoicos **27**, para construir el anillo de cicloheptano, característico de los hispananos. Los ácidos **27** se obtienen a partir de los alcoholes **20**, accesibles por adición del correspondiente organolitio o magnesiano a la amida **12**, seguido de reducción en las condiciones de Luche, o al aldehido **21**. Esta secuencia de reacciones ha resultado en la preparación, por primera vez, del esqueleto de hispanano **27a**. Con esta síntesis dirigida a obtener diversidad estructural es posible la obtención de una amplia variedad de derivados de tipo hispanano tales como **28b–28e**.*

ieved by Swern oxidation[14] followed by air oxidation of the obtained aldehydes. Friedel–Crafts cyclization of **17** was attempted by using the Eaton reagent (P_2O_5/$MeSO_3H$).[15] These conditions led to a clean transformation of compound **17** to a new product **18** having the phenyl group unchanged. A δ lactone structure was assigned for compound **18** on the spectroscopic results (Scheme 3). The configurations of C-8 and C-12 stereocenters were assigned from NOESY experiments. A clear correlation between H-12 (δ 6.19), H-8 (δ 2.80) was observed, which is compatible with a structure **18** having hydrogens H-12 and H-8 placed in same side of the plane defined by the lactone ring (Scheme 3).



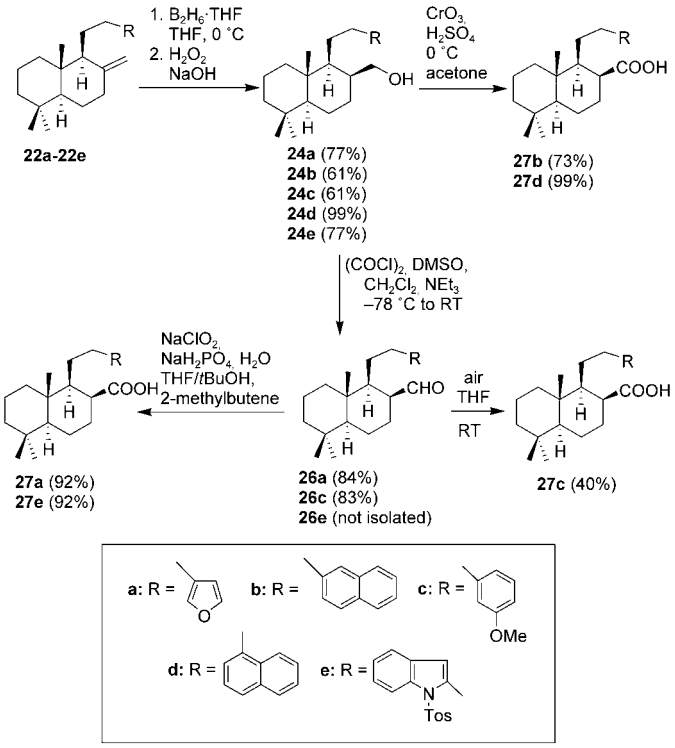
Scheme 3. Synthesis and Friedel–Crafts reaction of the 12-acetoxy-phenyllabdanic acid **17**.

Clearly, a C-12 oxygenated group is not compatible with a Friedel–Crafts ring closure on intermediates **9** (Scheme 2) to construct the desired seven-membered ring of the hispanane-like compounds **8**. Therefore, a desoxygenation step was introduced in the synthetic approach. More activated aromatic rings were also considered to ensure the success of the Friedel–Crafts reaction. Thus, ketones **19a–c** were prepared by addition of the corresponding lithium derivatives to Weinreb's amide **12**. Epimeric alcohols **20a–c** and *epi*-**20a–c** were obtained by reduction of the carbonyl groups under Luche conditions.[11] Additionally, alcohols **20d–e** and *epi*-**20d–e**, having a 1-naphthyl and 2-*N*-tosylindolyl substituents, respectively, were prepared by addition of the corresponding lithium reagents to aldehyde **21**. Alcohols **20** were submitted to the two-step Barton–McCombie[16] deoxygenation sequence. Reaction of the mixtures of alcohols with 1,1-thiocarbonyldiimidazol yielded the mixture of thioesters which was reduced by using TBTH/AIBN to form 12-desoxylabdane-like derivatives **22**, as single isomers in fair to excellent yields (Scheme 4).[17]



Scheme 4. Synthesis of the 12-desoxylabdane-like derivatives **22** from amide **12** *via* alcohols **20**.

The oxidative hydroboration (B_2H_6·THF followed by H_2O_2/NaOH work-up) of desoxylabdane derivatives **22a–e** resulted in the corresponding C-17 alcohols **24a–e** as single isomers.[18] The β-axial configuration of the hydroxymethyl group at carbon C-8 was assigned on analogous as described early for compounds **16** and *epi*-**16**,[10] and it is consistent with the double-bond hydroboration by the less-hindered α face of compounds **22**.[12] One-step oxidation to the corresponding 12-desoxylabdanic-like acids was achieved for compounds **27b** and **d** by using Jones reagent, while a two-step sequence was used for alcohols **24a**, **c** and **e**. Thus, aldehydes **26a**, **c** and **e** were obtained by either Swern or Jones oxidation and transformed to the 12-desoxylabdanic-like acids by air (**27c**) or by buffered $NaClO_2$ (**27a**, and **27e**) oxidation (Scheme 5).[19]



Scheme 5. Synthesis of 12-desoxylabdanic-like acids **27** by oxidation of alcohols **24**.

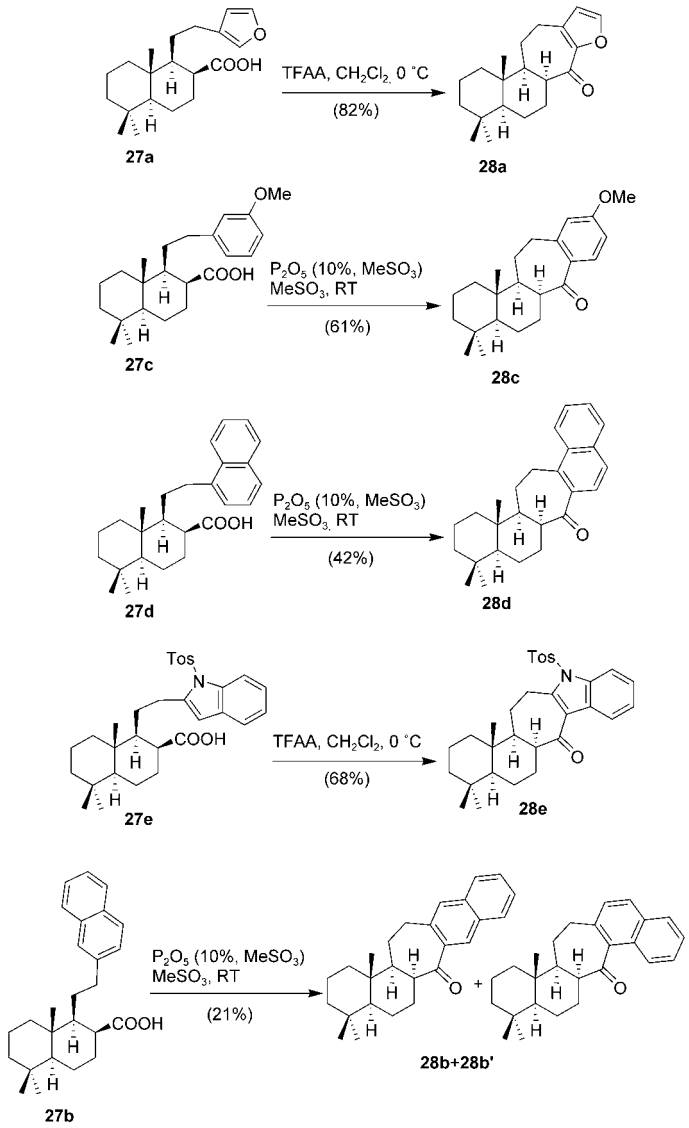
Friedel–Crafts cyclization of compounds **27a–e** was achieved either by using the Eaton's reagent[15] (compounds **27b–d**) or trifluoracetic anhydride (TFAA)[20] (compounds **28a** and **e**) to produce hispanane derivatives **28a–e** in good to excellent yields and as single isomers. The exception was the 2-naphtyl-derivative **27b** which gave a mixture of the two regioisomers **28b** and **28b′** in low yield (21%). The structure and regiochemistry of the products was unambiguously established by 1D and 2D NMR spectroscopic analyses. Table 1 shows the ^{13}C NMR spectra for the tetra- and pentacyclic derivatives **28a**, **28c–e**. It should be noted that compound **28a** has a tetracyclic hispanane skeleton with the correct natural stereochemistry. Therefore, the synthesis of compound **28a** represents the first entry to the skeleton of this natural product from (*R*)-(+)-sclareolide **1** in eight steps in 40% overall yield. Furthermore, the preparation of compounds **28b–e** demonstrates that our approach is fully applicable to prepare novel indole–hispanane and aromatic–hispanane natural product derivatives (Scheme 6). Particularly interesting is the hispanane–indol derivative **28e** since indole diterpenes are also found in nature.[22]

The flexibility of this diversity oriented approach to obtain hispanane-like derivatives is demonstrated by the preparation of the C-8 *epi*-hispanane derivatives. Thus, compound **28d** was prepared according to the general methodology depicted in Scheme 7, by simply introducing an additional epimerization step on intermediate aldehyde **26d**. This compound is available from alcohol **24d** through controlled Jones oxidation. Base epimerization produced compound *epi*-**26d** (70%) which was further oxidized with Jones reagent to yield acid *epi*-**27d**. The α-equatorial configuration of carbon C-17 acid *epi*-**27d** is in accord with the coupling constant values shown by H-8β axial (*epi*-**27d** δ 2.46, $J=12$ and 4 Hz). Compound *epi*-**27d** was cyclized to pentacyclic hispanane derivative *epi*-**28d** in 42% yield (Scheme 7). The β-axial configuration of the ketone carbon C-17, with respect to ring B, is based again on the coupling constant values of H-8β axial (*epi*-**27d** δ 3.05, $J=11.9$ and 3.8 Hz), as well as on the shift to low-field of the signal attributable to carbon C-6 with respect to hispanane **28d** ($\Delta\delta=+1.3$, see

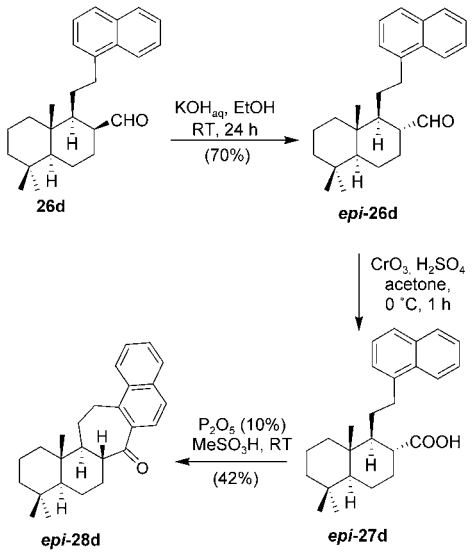
Table 1. ^{13}C NMR data for compounds **28a**, **28c**, **28d**, **28e** and *epi*-**28d**.[a]

	28a[b]	**28c**[c]	**28d**[b]	**28e**[d]	*epi*-**28d**[d]
C-1	38.6 t	39.1 t	39.8 t	39.0 t	38.8 t
C-2	18.4 t	18.5 t	18.5 t	18.4 t	18.7 t
C-3	42.0 t	42.1 t	42.1 t	42.0 t	41.9 t
C-4	33.2 q	33.2 s	33.1 s	33.1 s	33.2 s
C-5	56.1 d	55.8 d	55.4 d	55.8 d	50.7 d
C-6	19.5 t	19.7 t	19.8 t	19.5 t	21.1 t
C-7	27.7 t	28.6 t	27.6 t×2	27.8 t	29.6 t
C-8	46.8 d	47.3 d	47.8 d	48.2 d	51.6 d
C-9	51.8 d	51.6 d	51.7 d	51.0 d	54.7 d
C-10	39.1 s	38.8 s	38.6 s	38.8 s	38.4 s
C-11	24.0 t	27.0 t	27.6 t×2	28.0 t	28.4 t
C-12	28.0 t	34.1 t	28.4 t	24.8 t	26.0 t
C-17	190.8 s	202.7 s	205.6 s	200.0 s	210.5 s
C-18	33.5 q	33.6 q	33.7 q	33.6 q	33.6 q
C-19	21.6 q	21.7 q	21.9 q	21.6 q	21.8 q
C-20	13.6 q	13.9 q	14.0 q	13.8 q	14.7 q
C-13 (C-1′)	138.3 s	162.2 s	144.6 s	151.6 s	139.1 s
C-14 (C-2′)	113.3 d	148.0 s	136.1 s	136.1 s	133.6 s
C-15 (C-3′)	145.4 d	131.9 d	134.8 s	127.5 s	134.5 s
C-16 (C-4′)	150.7 s	130.9 s	132.3 s	125.2 d	131.5 s
C-5′		115.3 d	128.7 d	124.8 d	128.7 d
C-6′		111.6 d	127.4 d	122.6 s	127.0 d
C-7′			126.4 d x2	122.3 d	126.7 d
C-8′			125.2 d	114.4 d	126.6 d
C-9′			124.8 d		124.7 d
C-10′					124.2 d
C-OMe		55.3 q		21.7 q	
				145.5 s ph	
				136.2 s ph	
				130.1 d×2	
				126.4 d×2	

[a] Multiplicities were determined by DEPT experiments [b] Recorded at 125 MHz. [c] Recorded at 75 MHz. [d] Recorded at 50 MHz.



Scheme 6. Synthesis of hispanane **22a** and hispanane derivatives **28b–e** by Friedel–Crafts reaction of acids **27a–e**.

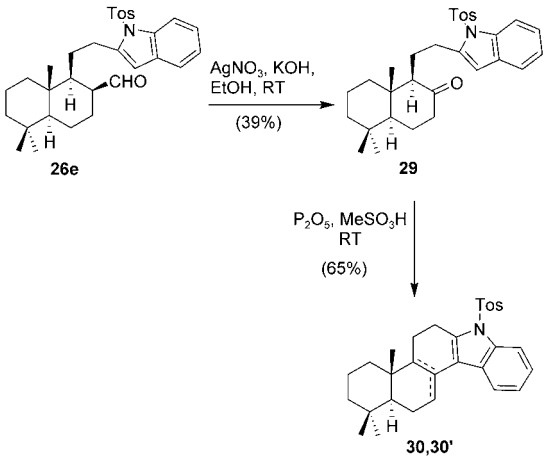


Scheme 7. Synthesis of the C-8 *epi*-hispanane derivative *epi*-**28d** from aldehyde *epi*-**26d**.

Table 1) Thus, the addition of an epimerization step, to the general sequence results in an entry to *epi*-series of hispanane derivatives.

Finally, the versatility of the Friedel–Crafts approach to hispanane-like derivatives developed above was further improved by the access of the 17-*nor*-hispanane–indol skeleton (Scheme 8). This time, ketone **29** was prepared by oxidative decarboxylation of aldehyde **26e** ($AgNO_3$/KOH/EtOH)[21] and submitted to Eaton's reagent to produce an inseparable mixture of 17-*nor*-hispanane–indol derivatives **30** and **30′**, which are isomers around the newly formed double bond. Formation of indolterpenes **30** and **30′** demonstrates that ketones can also be used as initiators for the Friedel–Crafts approach to hispanane and *nor*-hispanane derivatives. The two isomeric products **30** and **30′** should be formed by dehydration of the C-8 tertiary carbinol intermediate, which should be the primary product of the cyclization reaction.

In conclusion, we have developed a versatile entry to natural product derivatives with a hispanane skeleton, including the first building of the hispanane skeleton itself. The synthesis uses (*R*)-(+)-sclareolide **1** as the basic building scaffold and requires six or seven steps to produce the final compounds. The capacity of this approach to produce structurally diverse natural product derivatives is demonstrated by its application to the synthesis of hispanane–indol and hispanane–aromatic derivatives. By introducing an isomerization step on intermediate aldehyde **26**, the C-8 *epi*-hispanane series is also available. Application of this diversity oriented approach to yield the 17-*nor*-hispanane–indol skeleton has been demonstrated by using an oxidative decarboxylation step.



Scheme 8. Synthesis of the *nor*-hispanane derivative **30**, **30′** from ketone **29**.

Experimental Section

General methods: All procedures with air-sensitive reagents were carried out under dry argon atmosphere by using standard Schlenk techniques. All reagents were used as obtained from commercial sources. THF, and CH_2Cl_2 were distilled under positive pressure of argon from Na benzoquinone (THF) or CaH_2 (CH_2Cl_2). Other solvents were HPLC grade and were used without purification. Na_2SO_4 was used to remove water from the organic layer in reaction workups. Silica gel 60 F_{254} plates were used for TLC. Flash column chromatography was performed with silica gel (Merk, no. 9385, 230–400 mesh) and mixtures of AcOEt/hexanes or hexanes/CH_2Cl_2 as eluents. Melting points were determined on a Koffler block. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on a Varian Inova-300, Inova-400, Unity-500 and Bruker AM-200 spectrometers as specified. Chemical shifts for ^{1}H NMR are reported with respect to residual $CHCl_3$ (δ 7.25) and with respect to $CDCl_3$ (δ 77.0) for ^{13}C NMR spectra. MS were recorded in the positive EI mode (70 eV).

Synthesis of ketones 13 and 19a–c—General procedure: A solution of the corresponding magnesium or lithium reagent in THF was added under argon to a solution of amide **12** in THF at 0 °C. Lithium reagents were generated by halogen–metal exchange from the corresponding bromo-derivatives upon reaction with *n*BuLi at −78 °C. The mixtures were stirred until amide **12** disappeared (checked by TLC). The reaction was quenched by addition of aqueous NH_4Cl (saturated solution) and allowed to reach room temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The combined organic layers were dried and filtered, and solvents were removed under vacuum. Pure ketones were obtained after flash chromatography of the residues.

Alcohols 14 and, 20a–c and *epi*-20a–c—General procedure: In a typical experiment, $CeCl_3{\cdot}7H_2O$ (2 equiv) was added to a solution of ketone in MeOH at room temperature. The mixture was stirred until the cerium salt was dissolved, and then cooled at 0 °C. At this temperature $NaBH_4$ was added portionwise. When the starting material disappeared (by TLC), the excess of reagent was quenched by addition of H_2O and the mixtures were allowed to reach room temperature. MeOH was removed under vacuum and the residue was extracted with AcOEt. The combined organic layers were dried and filtered yielding a residue, which was purified by flash chromatography to yield the pure alcohols.

Alcohols 20d, *epi*-20d and 20e, *epi*-20e—General procedure: The solution of the respective lithium reagent in THF was added under argon to a solution of aldehyde **21** in THF at −78 °C. The lithium reagents were generated either by halogen–metal exchange from the corresponding bromo-derivatives or by hydrogen–metal exchange upon reaction with *n*BuLi at −78 °C. The mixture was stirred until aldehyde **21** disappeared (TLC). The reaction was quenched by addition of aqueous NH_4Cl saturated solution and allowed to reach room temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The combined organic layers were dried and filtered, and solvents removed under vacuum. Pure alcohols were obtained after flash chromatography of the residues.

Compounds 22a–e by desoxygenation of alcohols 20a–e, and *epi*-20a–e—General procedure: 1,1′-Thiocarbonyldiimidazole (3.5 equiv) was added to a solution of alcohols **20** in CH_2Cl_2. After the reagent was dissolved, most of the solvent was removed under vacuum and the reaction mixture was cooled to −20 °C. The crude reaction mixture was submitted to flash chromatography without any further treatment. The mixture of pure thioesters was immediately dissolved in degassed toluene under argon, followed by addition of $HSnBu_3$ (3 equiv) and a catalytic amount of AIBN. The mixture was heated under reflux until the esters disappeared (TLC). Then, the organic solvents were removed under vacuum and the residue was submitted to flash chromatography to give pure C-12 desoxygenated derivatives **22**.

Alcohols 16, *epi*-16 and 24 by hydroboration–oxidation of alkenes 1, *epi*-15 and 22a–e—General procedure: The respective alkene in THF was slowly added to a solution of $B_2H_6{\cdot}SMe_2$ or $B_2H_6{\cdot}$THF in THF at 0 °C. The mixture was stirred at room temperature until the starting material disappeared (TLC). Then, the mixture was cooled at 0 °C and H_2O_2 (33 % *v*/*v*) and NaOH (3 M) were successively added. After the reaction mixture was stirred for one additional hour, the solution was extracted with AcOEt. The combined organic layers were dried and filtered. The solvents were removed in vacuo and the residue was purified by flash chromatography to yield pure alcohols **16** and *epi*-**16** and **24a–e**.

Acids 27b and 27d by Jones oxidation of alcohols 24b and 24d: An excess of Jones reagent (persistence of orange color) was added dropwise to a solution of alcohol in acetone at 0 °C. The reaction mixture was stirred until the alcohol disappeared (TLC). The excess of the reagent was quenched by addition of MeOH; the mixture was allowed to reach room temperature and then diluted with H_2O. The organic solvents were removed under vacuum and the resulting residue was extracted with AcOEt. The combined organic layers were dried and filtered; the residue was purified by flash chromatography to yield the pure acid.

Acids 17, *epi*-17 and 27c by oxidation of alcohols 16, *epi*-16 and 24e—General procedure: A solution of $Cl_2(CO)_2$ in anhydrous CH_2Cl_2 was slowly added under argon to a solution of DMSO in anhydrous CH_2Cl_2 at −78 °C. After 15 min of stirring at this temperature, the mixture was added to a solution of the alcohol in CH_2Cl_2. After the reaction was completed (TLC), Et_3N was added. The resulting reaction mixture was allowed to reach room temperature; it was diluted with CH_2Cl_2 and washed with H_2O. The combined organic layers were dried and filtered. The removal of the solvents produced a residue which was dissolved in THF and air was bubbled through the solution. The solvents were removed in vacuo. The residue was purified by flash chromatography to afford the pure acid.

Acids 27a and 27e by $NaClO_2$ oxidation of aldehydes 26a and 26e—General procedure: An aqueous $NaClO_2$ solution (1.1 M) was added at 0 °C to a solution of the aldehyde in THF/*t*BuOH/2-methy-2-butene (1:2:1) in the presence of a $Na_2HPO_4{\cdot}H_2O$ buffer (6.9×10^{-1} M), and the mixture was allowed to reach room temperature slowly. Then, HCl (10 % *v*/*v*) was added, organic solvents were removed under vacuum and the residue was extracted with AcOEt. The combined organic layers were dried and filtered. The solvents were removed and the residie was purified by flash chromatography to yield the pure acids.

General procedures for Friedel–Crafts acylations—Method A: The respective acid **27** in methanesulfonic acid or CH_2Cl_2 was added to a solution of P_2O_5 (10 %) in methanesulfonic acid at room temperature. The mixture was stirred until the starting material was consumed (TLC). The reaction mixture was poured into a solution of saturated $NaHCO_3$ and the aqueous layer was separated and extracted with AcOEt. Reaction product was purified by column chromatography.

Method B: A solution of trifluoracetic anhydride in CH_2Cl_2 was slowly added to solution of respective acid **27** in CH_2Cl_2 at 0 °C. The mixture was stirred until the acid was consumed, then the reaction mixture was poured into $NaHCO_3$ saturated solution and the aqueous layer was extracted with AcOEt. The residues were purified by column chromatography to yield the pure reaction products as described above.

Compound 28a by Friedel–Crafts reaction of acid 27a (method B): A solution of acid **27a** (15.0 mg, 0.05 mmol) in CH_2Cl_2 at 0 °C was treated with a solution of trifluoroacetic acid in CH_2Cl_2 (50 μL, 1.4×10^{-3} M). After 10 min of stirring, acid **27a** had been consumed and the reaction mixture was worked-up according to the general procedure. Chromatography of the residue by using hexanes/AcOEt 95:5 yielded pure **28a** (9.6 mg, 68 %) as a white crystalline solid. M.p. 184–186 °C; $[\alpha]_D^{20} = +45.5$ (c = 0.07 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.47 (d, ^3J = 1.7 Hz, 1H; H-15), 6.35 (d, ^3J = 1.7 Hz, 1H; H-14), 2.81 (ddd, ^2J = 15.8, ^3J = 5.8, ^3J = 1.7 Hz, 1H; H_B-12), 2.75 (br t, ^3J = 5.5 Hz, 1H; H-8α), 2.50 (m, 2H; H_A-12), 2.17 (dddd, J = 15, J = 8.9, J = 5.9, J = 1.7 Hz, 1H; H-11), 1.96 (td, J = 9.5, J = 6.4 Hz, 1H; H-9α), 1.76 (qd, J = 13.4, J = 3.8 Hz, 1H; H-7α), 1.65 (m, 1H), 1.48–1.20 (m, 8H), 1.114 (td, J = 12.8, J = 4.7 Hz, 1H; H-3α), 0.95 (dd, J = 5.8, J = 2.8 Hz, 1H; H-5α), 0.92–0.87 (m, 2H), 0.87 (s, 3H; CH_3-18), 0.79 (s, 3H; CH_3-19), 0.62 (s, 3H; CH_3-20); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 190.8 (s, C-17), 150.7 (s, C-16), 145.4 (d, C-15), 138.3 (s, C-13), 113.3 (d, C-14), 56.1 (d, C-5), 51.8 (d, C-9), 46.8 (d, C-8), 42.0 (t, C-3), 39.1 (s, C-10), 38.6 (t, C-1), 33.5 (q, C-18), 33.2 (s, C-4), 28.0 (t, C-12), 27.7 (t, C-7), 24.0 (t, C-11), 21.6 (q, C-19), 19.5 (t, C-6), 18.4 (t, C-2), 13.6 (q, C-20); IR (nujol): $\tilde{\nu}$ = 2924, 2854, 1654, 1582,

1480, 1458, 1428, 1384, 1265, 1241, 886, 792 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 300 (13) $[M]^+$, 285 (1), 176 (5), 163 (32), 149 (47), 136 (9), 91 (9), 58 (35), 43 (100); elemental analysis calcd (%) for $C_{20}H_{28}O_2$: C 79.96, H 9.39; found: C 79.87, H 9.24.

Compounds 28b, 28b′ by Friedel–Crafts reaction of acid 27b (method A): Acid **27b** (20.0 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of P_2O_5 (15 mg) in methanesulfonic acid (1.0 mL). The reaction was stirred at room temperature for 1 h and it was heated under reflux for another 30 min until the starting material was consumed. After workup as above, a mixture of pure **28b** and **28b′** (4.0 mg, 21%) was obtained as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.01$ (s, 1H; H-Ar), 7.86 (d, $^3J = 7$ Hz, 1H, H-Ar), 7.83–7.75 (m, 4H; H-Ar), 7.52–7.32 (m, 5H; H-Ar), 3.21–2.7 (m, 6H), 2.01–1.01 (m, 28H), 0.97(s, 3H; CH_3-18-isomer A), 0.88 (s, 3H; CH_3-18-isomer B), 0.84 (s, 3H; CH_3-19-isomer A), 0.82 (s, 3H; CH_3-20-isomer A), 0.80 (s, 3H; CH_3-19-isomer B), 0.77 (s, 3H; CH_3-20-isomer B); MS (70 eV, EI): *m*/*z* (%): 360 (100) $[M]^+$, 345 (6), 332 (27), 236 (7), 223 (47), 209 (54), 196 (37), 181 (25), 168 (29), 152 (13), 140 (33), 123 (7),109 (8), 95 (12), 81 (10), 69 (14), 55 (14), 41 (14).

Compound 28c by Friedel–Crafts reaction of acid 27c (method A): Acid **27c** (8 mg, 0.02 mmol) in methanesulfonic acid (0.5 mL) was added to a solution containing P_2O_5 (10 mg) in methanesulfonic acid (1 mL). The reaction was completed after 10 min of stirring. After workup as described above, a residue was purified by chromatography with hexanes/AcOEt 95:5 to yield pure **28c** (4.6 mg, 61%) as white solid. M.p. 174–177 °C; $[\alpha]_D^{23} = +16.4$ ($c = 0.07$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.09$ (d, $^3J = 8.8$ Hz, 1H; H-Ar), 6.70 (dd, $^3J = 8.8$, $^4J = 2.7$ Hz, 1H; H-Ar), 6.72 (d, $^4J = 2.4$ Hz, 1H; H-Ar), 3.83 (s, 3H; MeO-Ar), 3.07 (d, $^2J = 15.6$ Hz, 1H; H_B-12), 3.03 (br t, $^3J = 6.1$ Hz, 1H; H-8), 2.90 (dd, $^2J = 15.4$, $^3J = 6.6$ Hz, 1H; H_A-12), 2.36 (br d, $^2J = 13.2$ Hz, 1H; H-7β), 2.20 (quin, $J = 6.8$ Hz, 1H; H_B-11), 1.86 (m, overlapped 2H; H-9+ H-7α), 1.62 (ddq, $^2J = 13.4$, $^3J = 2.7$, $^3J = 2.3$ Hz, 1H; H-2α), 1.55–1.10 (overlapped m, 7H), 0.90 (overlapped m, 2H), 0.88 (s, 3H; CH_3-18), 0.82 s, 3H; CH_3-19), 0.66 (s, 3H; CH_3-20); ^{13}C NMR (75.1 MHz, $CDCl_3$): $\delta = 202.7$ (s, C-17), 162.2 (s, C-Ar), 148.0 (s, C-Ar), 131.9 (d, C-Ar), 130.9 (s, C-Ar), 115.3 (d, C-Ar), 111.6 (d, C-Ar), 55.8 (d, C-5), 55.3 (q, MeO-Ar), 51.6 (d, C-9), 47.3 (d, C-8), 42.1 (t, C-3), 39.1 (t, C-1), 38.8(s, C-10), 34.1 (t, C-12), 33.6 (q, C-18), 33.2 (s, C-4), 28.6 (t, C-7), 27.0 (t, C-11), 21.7 (q, C-19), 19.7 (t, C-6), 18.5 (t, C-2), 13.9 (q, C-20); IR (nujol): $\tilde{\nu} = 2924$, 2854, 1663, 1601, 1461, 1265, 1226, 1106, 1034, 967, 815 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 340 (25) $[M]^+$, 325 (2), 215 (7), 203 (51), 189 (100), 176 (28), 161 (18), 148 (28), 91 (21), 81 (14), 69 (23), 55 (27), 41 (31); elemental analysis calcd (%) for $C_{23}H_{32}O_2$: C 81.13, H 9.47; found: C 80.94, H 9.32.

Compound 28d by Friedel–Crafts reaction of acid 27d (method A): Acid **27d** (20 mg, 0.05 mmol) in CH_2Cl_2 (0.5 mL) was added to a solution of P_2O_5 (15 mg) in methanesulfonic acid (1 mL) at room temperature. The reaction was completed after 5 h of stirring (TLC). The residue was purified by chromatography with hexanes/CH_2Cl_2 9:1 to yield pure **28d** (4.0 mg, 42%) as a white crystalline solid. M.p. 159–161 °C; $[\alpha]_D^{21} = -12.5$ ($c = 0.12$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 8.27$ (dd, $J = 6.2$, $J = 3.6$ Hz, 1H; H-Ar), 8.09 (d, $^3J = 8.7$ Hz, 1H; H-Ar), 7.83 (dd, $^3J = 6.2$, $^4J = 3.6$ Hz, 1H; H-Ar), 7.72 (d, 1H, $J = 8.7$ Hz, H-Ar), 7.55 (dd, 1H, $J = 9.6$, $J = 3.2$ Hz, H-Ar), 7.54 (dd, $J = 9.8$, $J = 3.6$ Hz, 2H; H-Ar), 4.00 (dd, $^2J = 17$, $^3J = 7$ Hz, 1H; H_B-12), 3.28 (t, $^3J = 6.8$ Hz, 1H; H-8), 3.05 (dd, $^2J = 17$, $^3J = 11.7$ Hz, 1H; H_A-12), 2.38 (q, $^2J = {}^3J = 7.2$ Hz, 1H; H_B-11), 2.30 (br d, $^2J = 13.4$ Hz, 1H), 1.93 (dd, $^3J = 8.7$, $^3J = 3.8$ Hz, 1H; H-9), 1.90 (overlapped m, 2H), 1.89–0.93 (m, 9H), 0.91 (s, 3H; CH_3-18), 0.87 (s, 3H; CH_3-19), 0.80 (s, 3H; CH_3-20); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 205.6$ (s, C-17), 144.6 (s, C-Ar), 136.1 (s, C-Ar), 134.8 (s, C-Ar), 132.3 (s, C-Ar), 128.7 (d, C-Ar), 127.4 (d, C-Ar), 126.4 (d, 2C-Ar), 125.2 (d, C-Ar), 124.8 (d, C-Ar), 55.4 (d, C-5), 51.7 (d, C-9), 47.8 (d, C-8), 42.1 (t, C-3), 39.8 (t, C-1), 38.6 (s, C-10), 33.7 (q, C-18), 33.1 (s, C-4), 28.4 (t, C-12), 27.6 (2t, C-7, C-11), 21.9 (q, C-19), 19.8 (t, C-6), 18.5 (t, C-2), 14.0 (q, C-20); IR (nujol): $\tilde{\nu} = 2925$, 2854, 1668, 1462, 1377, 1217, 1102, 1032, 813, 765, 747 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 360 (88) $[M]^+$, 345 (5), 332 (5), 223 (52), 209 (100), 196 (33), 181 (20), 168 (29), 152 (16), 140 (34), 123 (7), 109 (7), 95 (12), 81 (11), 69 (16), 55 (18), 41 (18); elemental analysis calcd (%) for $C_{26}H_{32}O$: C 86.62, H 8.95; found: C 86.28, H 8.70.

Compound 28e by Friedel–Crafts reaction of acid 27e (method B): Trifluoroacetic anhydride (60 μL, 0.7×10^{-3} M) in CH_2Cl_2 was added at 0 °C to a solution of acid **27e** (19 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL). The starting material was consumed after 3 h of stirring. Workup as described above, yielded a residue which was purified by chromatography by using hexanes/AcOEt 95:5; the pure compound **28e** (15 mg, 82%) was obtained as a white crystalline solid. M.p. 169–171 °C; $[\alpha]_D^{20} = -11.2$ ($c = 0.12$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.43$ (m, 1H; H-Ar), 8.21 (m, 1H; H-Ar), 7.65 (d, $^3J = 8.4$ Hz, 2H; H-Ar), 7.32 (m, 2H; H-Ar), 7.23 (d, $J = 8.1$ Hz, 2H; H-Ar), 4.09 (dd, $^2J = 16.4$, $^3J = 5.4$ Hz, 1H; H_B-12), 2.87 (t, $^3J = 6$ Hz, 1H; H-8), 2.71 (dd, $^2J = 16.5$, $^3J = 12.3$ Hz, 1H; H_A-12), 2.42 (br d, $J = 13.5$ Hz, 1H; H-3α), 2.36 (s, 3H; CH_3-Ar), 2.23 (quin, $J = 7$ Hz, 1H; H_B-11), 1.89 (ddd, $J = 15.6$, $J = 11.9$, $J = 7.9$ Hz, 1H; H-9), 1.78 (td, $J = 13.3$, $J = 3.9$ Hz, 1H; H-7α), 1.62 (m, 1H), 1.49–1.30 (m, 7H), 1.15 (td, $J = 12.5$, $J = 3.7$ Hz; 1H), 0.94 (dd, $J = 12.5$, $J = 2.4$ Hz, 1H; H-5α), 0.88 (s, 3H; CH_3-18), 0.81 (s, 3H; CH_3-19), 0.63 (s, 3H; CH_3-20); ^{13}C NMR (50.3 MHz, $CDCl_3$): $\delta = 200.0$ (s, C-17), 151.6 (s, C-Ar), 145.5 (s, C-Ar), 136.2 (s, C-Ar), 136.1 (s, C-Ar), 130.1 (d, 2C-Ar), 127.5 (s, C-Ar), 126.4 (d, 2C-Ar), 125.2 (d, C-Ar), 124.8 (d, C-Ar), 122.6 (s, C-Ar), 122.3 (d, C-Ar), 114.4 (d, C-Ar), 55.8 (d, C-5), 51.0 (d, C-9), 48.2 (d, C-8), 42.0 (t, C-3), 39.0 (t, C-1), 38.8 (s, C-10), 33.6 (q, C-18), 33.1 (s, C-4), 28.0 (t, C-11), 27.8 (t, C-7), 24.8 (t, C-12), 21.7 (q, Me-Ar), 21.6 (q, C-19), 19.5 (t, C-6), 18.4 (t, C-2), 13.8 (q, C-20); IR (nujol): $\tilde{\nu} = 2924$, 2854, 1668, 1460, 1371, 1165, 1055, 990, 760 cm^{-1}; MS (70 eV, EI): *m*/*z* (%): 503 (11) $[M]^+$, 366 (6), 352 (23), 320 (4), 220 (8), 196 (16), 180 (15), 167 (23), 155 (27), 130 (26), 91 (100), 81 (19), 69 (38), 55 (33), 41 (34); elemental analysis calcd (%) for $C_{31}H_{37}NO_3S$: C 73.92, H 7.40; found: C 73.79, H 7.27.

Aldehyde 26d by oxidation of alcohol 24d: Alcohol **24d** (248 mg, 0.68 mmol) in acetone (30 mL) was treated with Jones reagent for 2 h. Workup as described yielded a residue which was purified by flash chromatography with hexanes/CH_2Cl_2 (4:1) to produce pure aldehyde **26d** (230 mg, 94%) as a white amorphous solid. M.p. 106–108 °C; $[\alpha]_D^{21} = +4.13$ ($c = 0.41$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 10.11$ (s, 1H; H-17), 8.03 (d, $^3J = 8.1$ Hz, 1H; H-Ar), 7.86 (d, $^3J = 7.8$ Hz, 1H; H-Ar), 7.72 (d, $^3J = 8.1$ Hz, 1H; H-Ar), 7.58–7.30 (overlapped m, 4H; H-Ar), 3.34 (ddd, $^2J = 13.4$, $^3J = 10.2$, $^3J = 6.8$ Hz, 1H; H_A-12), 2.99 (ddd, $^2J = 13.4$, $^3J = 9.5$, $^3J = 6.3$ Hz, 1H; H_B-12), 2.70 (t, $^3J = 4.6$ Hz, 1H; H-8), 2.40 (br dd, $J = 7.6$ Hz, $J = 4.6$ Hz, 1H; H-7α), 2.05 (dd, $J = 6.4$, $J = 3.7$ Hz, 1H; H-9), 2.02 (dd, $J = 8.5$, $J = 6.8$ Hz, 1H; H-11), 1.70–1.10 (overlapped m, 10H), 0.94 (dd, $J = 11.5$, $J = 2.6$ Hz, 1H; H-5), 0.86 (s, 3H; CH_3), 0.77 (s, 3H; CH_3), 0.68 (s, 3H; CH_3); ^{13}C NMR (75.3 MHz, $CDCl_3$): $\delta = 205.2$ (d, C-17), 138.7 (s, C-Ar), 133.9 (s, C-Ar), 131.7 (s, C-Ar), 128.8 (d, C-Ar), 126.7 (d, C-Ar), 126.0 (d, C-Ar), 125.9 (d, C-Ar), 125.6 (d, C-Ar), 125.5 (d, C-Ar), 123.6 (d, C-Ar), 55.7 (d, C-5), 54.5 (d, C-9), 47.5 (d, C-8), 41.9 (t, C-1), 38.6 (t+s, C-3+C-10), 33.5 (q, C-18), 33.3 (s, C-4), 32.3 (t, C-12), 26.9 (t, C-7), 26.6 (t, C-11), 21.5 (q, C-19), 18.8 (t, C-6), 18.6 (t, C-2), 15.4 (q, C-20); MS (70 eV, EI): *m*/*z* (%): 362 (66) $[M]^+$, 344 (3), 331 (4), 170 (15), 167 (16), 154 (32), 141 (100), 123 (13), 115 (17), 107 (4), 95 (10), 81 (10), 69 (15), 55 (10), 41 (9); elemental analysis calcd (%) for $C_{26}H_{34}O$: C 86.13, H 9.45; found: C 85.94, H 9.38.

Aldehyde *epi*-26d by epimerization of aldehyde 26d: A solution of aldehyde **26d** (50 mg, 0.14 mmol) in EtOH (3.5 mL) at room temperature was treated with an aqueous solution of KOH (2.0 mL, 6×10^{-2} M). After 24 h of stirring the reaction mixture was filtered through a pad of Celite, diluted with water (10 mL) and extracted with AcOEt (3×20 mL). Workup as described yielded a residue which after chromatography with hexanes/AcOEt 95:5 produced pure *epi*-**26d** (30 mg, 70%) as a colorless syrup. $[\alpha]_D^{23} = +28.6$ ($c = 0.28$ in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 9.61$ (d, $^3J = 4.6$ Hz, 1H; H-17), 7.93 (d, $^3J = 8.2$ Hz, 1H; H-Ar), 7.81 (dd, $J = 7.5$, $J = 1.8$ Hz, 1H; H-Ar), 7.68 (d, $J = 7.9$ Hz, 1H; H-Ar), 7.56 (overlapped m, 4H; H-Ar), 3.16–2.84 (m, 3H), 2.44–2.31 (m, 1H), 1.9–0.93 (m, 13H), 0.89 (s, 3H; CH_3-18), 0.83 (s, 3H; CH_3-19), 0.80 (s, 3H; CH_3-20); ^{13}C NMR (75.3 MHz, $CDCl_3$): $\delta = 205.3$ (d, C-17), 138.7 (s, C-Ar), 133.8 (s, C-Ar), 131.6 (s, C-Ar), 128.7 (d, C-Ar), 126.6 (d, C-Ar), 126.0 (d, C-Ar), 125.9 (d, C-Ar), 125.6 (d, C-Ar), 125.4 (d, C-Ar), 123.7 (d, C-Ar), 54.6 (d, C-5), 54.2 (d, C-9), 51.0 (d, C-8), 42.0 (t, C-1), 38.5 (t, C-3), 37.9 (s, C-10), 34.4 (t, C-12), 33.4 (q, C-18), 33.2 (s, C-4), 30.9 (t, C-7), 26.7 (t, C-11), 21.7 (q, C-19), 20.1 (t, C-6), 18.6 (t, C-2), 14.1 (q, C-20);

IR (nujol): $\tilde{\nu}$ =2924, 2853, 2715, 1724, 1596, 1462, 1376, 798 cm^{-1}; MS (70 eV, EI): *m/z* (%): 362 (14) $[M]^+$, 348 (3), 332 (2), 179 (7), 170 (7), 154 (34), 141 (100), 115 (16), 95 (11), 81 (12), 69 (26), 55 (20), 41 (20); elemental analysis calcd (%) for $C_{26}H_{34}O$: C 86.13, H 9.45; found: C 86.09, H 9.40.

Acid *epi*-27d by Jones oxidation of aldehyde *epi*-26d: Aldehyde *epi*-**26d** (25 mg, 0.07 mmol) in acetone (2.0 mL) was treated with the Jones reagent for 1 h. Workup as described yielded a residue which after flash chromatography with hexanes/AcOEt 9:1 produced pure *epi*-**27d** (17 mg, 65%) as colorless syrup. $[\alpha]_D^{22}$ = +14.1 (c=1.49 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.96 (dd, ^3J=9.2, ^4J=1.5 Hz, 1H; H-Ar), 7.78 (dd, ^3J=7.5, ^4J=2.0 Hz, 1H; H-Ar), 7.61 (dd, ^3J=7.7, ^4J=1.5 Hz 1H; H-Ar), 7.40 (m, 2H; H-Ar), 7.24 (m, 2H; H-Ar), 3.19 (td, ^3J=13, ^3J=4.9 Hz, 1H; H_A-12), 2.93 (td, ^2J=^3J=13, ^3J=5.7 Hz, 1H; H_B-12), 2.46 (td, ^3J=12, ^3J=4 Hz, 1H; H-8), 2.06 (m, 1H), 1.99–0.90 (m, 13H), 0.87 (s, 3H; CH_3), 0.81 (s, 3H; CH_3), 0.79 (s, 3H; CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ =183.2 (s, C-17), 139.1 (s, C-Ar), 133.8 (s, C-Ar), 131.7 (s, C-Ar), 128.6 (d, C-Ar), 126.4 (d, C-Ar), 125.8 (d, C-Ar), 125.7 (d, C-Ar), 125.5 (d, C-Ar), 125.3 (d, C-Ar), 123.8 (d, C-Ar), 54.6 (d, C-5), 52.6 (d, C-9), 47.2 (d, C-8), 42.0 (t, C-3), 38.4 (t, C-1), 38.1 (s, C-10), 34.8 (t, C-12), 33.4 (q, C-18), 33.2 (s, C-4), 31.7 (t, C-7), 30.9 (t, C-11), 21.7 (q, C-19), 20.7 (t, C-6), 18.6 (t, C-2), 14.0 (q, C-20); IR (film): $\tilde{\nu}$ =2923 (broad), 1694, 1596, 1511, 1455, 1398, 1215, 796 cm^{-1}; MS (70 eV, EI): *m/z* (%): 378 (78) $[M]^+$, 363 (6), 167 (11), 154 (19), 141 (100), 123 (15), 109 (7), 95 (9), 81 (9), 69 (18), 55 (14), 41 (14); elemental analysis calcd (%) for $C_{26}H_{34}O_2$: C 82.49, H 9.05; found: C 82.33, H 8.87.

Compound *epi*-28d by Friedel–Crafts reaction of acid *epi*-27d: Acid *epi*-**27d** (20 mg, 0.05 mmol) in methanesulfonic acid (0.5 mL) was treated with a solution of P_2O_5 (15 mg) in methanesulfonic acid (1.0 mL) at room temperature. The mixture was stirred for 5 h. The residue which was obtained following the general procedure was purified by chromatography with hexanes/CH_2Cl_2 4:1 to yield unreacted acid (10 mg) and pure ketone *epi*-**28d** (4 mg, 42% based on recovered acid) as a colorless syrup. $[\alpha]_D^{22}$ = +28.7 (c=0.60 in $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.14 (dd, ^3J=8.9, ^4J=1.7 Hz, 1H; H-Ar), 7.84 (dd, ^3J=9.2, ^4J=2.3 Hz, 1H; H-Ar), 7.71 (d, ^3J=8.5 Hz, 1H; H-Ar), 7.57 (d, ^3J=8.5 Hz, 1H; H-Ar), 7.53 (overlapped m, 2H; H-Ar), 3.61 (ddd, ^2J=17.4, ^3J=7.4, ^3J=3.4 Hz, 1H; H_B-12), 3.21 (ddd, ^2J=17, ^3J=10, ^3J=3 Hz 1H; H_A-12), 3.05 (td, J=11.9 Hz, J=3.8 Hz, 1H; H-8), 2.10–1.20 (m, 9H), 1.12 (td, J=13.2 Hz, J=3.8 Hz, 1H), 1.00 (s, 3H; CH_3-18), 0.90 (overlapped m, 3H), 0.83 (s, 3H; CH_3-19), 0.82 (s, 3H; CH_3-20); ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 210.5 (s, C-17), 139.1 (s, C-Ar), 133.6 (s, C-Ar), 134.5 (s, C-Ar), 131.5 (s, C-Ar), 128.7 (d, C-Ar), 127.0 (d, C-Ar), 126.7 (d, C-Ar), 126.6 (d, C-Ar), 124.7 (d, C-Ar), 124.2 (d, C-Ar), 54.7 (d, C-5), 51.6 (d, C-8), 50.7 (d, C-9), 41.9 (t, C-3), 38.8 (t, C-1), 38.4 (s, C-10), 33.6 (q, C-18), 33.2 (s, C-4), 29.6 (t, C-7), 28.4 (t, C-11), 26.0 (t, C-12), 21.8 (q, C-19), 21.1 (t, C-6), 18.7 (t, C-2), 14.7 (q, C-20); IR (KBr): $\tilde{\nu}$=2922, 2847, 1664, 1459, 1386, 1260, 1219, 1158, 1087, 1036, 818, 801, 759, 741 cm^{-1}; MS (70 eV, EI): *m/z* (%): 360 (35) $[M]^+$, 332 (7), 223 (31), 209 (39), 196 (39), 178 (39), 168 (62), 152 (41), 140 (100), 95 (33), 81 (31), 69 (58), 55 (68), 41 (77); elemental analysis calcd (%) for $C_{26}H_{32}O$: C 86.62, H 8.95; found: C 86.49, H 8.83.

Ketone 29 by oxidation of alcohol 24e: Alcohol **24e** (40 mg, 0.08 mmol) in acetone (2 mL) was treated with Jones reagent for 15 min. Working in the usual way a residue was obtained which, without any further purification, was dissolved in dry ethanol (2 mL) and cooled to 0°C. The mixture was treated consecutively with $AgNO_3$ aqueous solution (1.0 mL, 6×10^{-3} M) and aqueous KOH (1.0 mL, 7×10^{-3} M). After 15 min of stirring, the mixture was filtered through a pad of Celite. Aqueous HCl was added until pH 1 and the mixture was extracted with $CHCl_3$ (3×20 mL). The residue obtained in the usual way was purified by chromatography with hexanes/AcOEt 95:5 to yield pure ketone **29** (15 mg, 39%) as colorless syrup. $[\alpha]_D^{23}$ = +42.5 (c=0.35 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=8.14 (d, ^3J=8.3 Hz, 1H; H-Ar), 7.58 (d, ^3J=8.3 Hz, 2H; H-Ar), 7.38 (d, ^3J=7.9 Hz, 1H; H-Ar), 7.22 (td, ^3J=8.3, ^4J=1.5 Hz, 1H; H-Ar), 7.18 (t, ^3J=8.3 Hz, 1H; H-Ar), 7.15 (d, ^3J=8.1 Hz, 2H; H-Ar), 6.40 (s, 1H; H-Ar), 3.05 (ddd, ^2J=14.9, ^3J=9.7, ^3J=5.1 Hz, 1H; H_B-12), 2.80 (ddd, ^2J=14.9, ^3J=8.7, ^3J=6.6 Hz, 1H; H_A-12), 2.43 (ddd, ^2J=13.2, ^3J=4.9, ^3J=2.1 Hz, 1H; H-7β), 2.30 (overlapped m, 1H; H-6α), 2.31 (s, 3H, CH_3-Ar), 2.16 (d, J=9.8 Hz, 1H; H-9), 2.04 (m, 2H), 1.77 (overlapped m), 1.66 (qd, J=13.4 Hz, J=5.1 Hz, 1H; H-6β), 1.5–1.3 (m, 4H), 1.25–1.03 (m, 3H), 0.95 (s, 3H; CH_3), 0.84 (s, 3H; CH_3), 0.73 (s, 3H; CH_3); ^{13}C NMR (75.3 MHz, $CDCl_3$): δ=212.3 (s, C-8), 144.6 (s, C-Ar), 142.4 (s, C-Ar), 137.2 (s, C-Ar), 136.1 (s, C-Ar), 129.9 (s, C-Ar), 129.8 (d, 2C-Ar), 126.3 (d, 2C-Ar), 123.8 (d, C-Ar), 123.5 (d, C-Ar), 120.1 (d, C-Ar), 114.9 (d, C-Ar), 109.2 (d, C-Ar), 63.4 (d, C-9), 54.1 (d, C-5), 42.7 (s, C-10), 42.6 (t, C-7), 41.8 (t, C-3), 39.1 (t, C-1), 33.7 (s- C-4), 33.5 (q, C-18), 28.2 (t, C-12), 24.0 (t, C-11), 21.7 (q, *Me*-Ar), 21.6 (q, C-19), 21.5 (t, C-6), 19.0 (t, C-2), 14.8 (q, C-20); IR (KBr): $\tilde{\nu}$ =2925, 2850, 1707, 1597, 1452, 1368, 1175, 1145, 1091, 1053, 811, 748 cm^{-1}; MS (70 eV, EI): *m/z* (%): 491 $[M]^+$ (2), 366 (3), 350 (4), 336 (100), 318 (7), 297 (14), 285 (24), 233(10), 220 (21), 198 (10), 180 (9), 168 (6), 156 (14), 143 (19), 130 (58), 109 (6), 91 (40), 69 (17), 55 (16), 41 (12); elemental analysis calcd (%) for $C_{30}H_{37}NO_3S$: C 73.28, H 7.58; found: C 72.97, H 7.61.

Compounds 30, 30′ by Friedel–Crafts reaction of ketone 29 (method A): Ketone **29** (8.0 mg, 0.02 mmol) in methanesulfonic acid (0.5 mL) was added to a solution of P_2O_5 (5.0 mg) in methanesulfonic acid (0.5 mL) at room temperature. The reaction mixture was stirred for 10 min. The residue obtained after the usual workup was purified by chromatography with hexanes/AcOEt 97:3 to yield a pure mixture of **30** and **30′** (5.0 mg, 65%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.36 (d, ^3J=8.4 Hz, 1H), 8.21 (dd, ^3J=7, ^4J=1.9 Hz, 1H), 8.14 (d, ^3J=8.8 Hz, 1H), 8.03 (d, J=7.6 Hz, 1H), 7.83 (dd, J=7.1 Hz, J=1.8 Hz, 1H), 7.70 (d, J=8.3 Hz, 2H), 7.62 (d, J=8.3 Hz, 2H), 7.42 (dd, J=7.3 Hz, J=1.9 Hz, 1H), 7.25 (m, 2H), 7.16 (d, J=8.4 Hz, 2H), 7.09 (d, J=8.3 Hz, 2H), 6.44 (t, J=2.6 Hz, 1H), 3.41 (m, 2H), 3.19 (ddd, J=19.0 Hz, J=11.4 Hz, J=7.6 Hz, 1H), 2.81 (ddd, J=19.0 Hz, J=12.0 Hz, J=6.6 Hz, 1H), 2.37 (broad d, J=13.3 Hz, 1H), 2.32 (s, 3H; CH_3-Ar), 2.26 (s, 3H; CH_3-Ar), 0.97 (s, 3H; CH_3), 0.95 (s, 3H; CH_3), 0.94 (s, 3H; CH_3), 0.89 (s, 6H; $2CH_3$), 0.85 (s, 3H; CH_3); IR (KBr): $\tilde{\nu}$ =2924, 2854, 1598, 1460, 1376, 1175, 1153, 1091, 1003, 811, 743, 659 cm^{-1}; MS (70 eV, EI): *m/z* (%): 473 $[M]^+$ (100), 456 (61), 360 (25), 318 (68), 300 (1), 232 (29), 217 (27), 206 (20), 194 (48), 91 (31), 69 (9), 55 (7), 41 (5).

Acknowledgements

Financial support by the Spanish Ministerio de Ciencia y Tecnología (Grants No. BQU2001-1283, CTQ2004-06250-C02-02/BQU (M.C.T.) and CTQ2004-06250-C02-01/BQU (M.A.S.)) and by the Consejería de Educación (Comunidad de Madrid, Grants No. 07M/0044/2002 to M.C.T. and 07 M/0043/2002 to M.A.S.) is gratefully acknowledged. I. García thanks the MCyT (Spain) for a FPI-predoctoral fellowship.

[1] M. D. Burke, S. L. Schreiber, *Angew. Chem.* **2003**, *115*, 48–60; *Angew. Chem. Int. Ed.* **2003**, *42*, 46–58.
[2] a) F. Guillier, D. Orain, M. Bradley, *Chem. Rev.* **2000**, *100*, 2091–2158; b) L. A. Thompson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555–600; c) *Combinatorial Chemistry and Molecular Diversity in Drug Discovery* (Eds.: E. M. Gordon, J. F. Kerwin, Jr.), Wiley, New York, **1998**; d) J. Stetter, F. Lieb, *Angew. Chem.* **2000**, *112*, 1792–1812; *Angew. Chem. Int. Ed.* **2000**, *39*, 1724–1744.
[3] The reactivity of densely functionalized natural products is a challenging arena to encounter new and unexpected transformations, due to the singular array of functionalities presented by many of these compounds.
[4] a) L. F. Tietze, H. P. Bell, S. Chandrasekhar, *Angew. Chem.* **2003**, *115*, 4128–4160; *Angew. Chem. Int. Ed.* **2003**, *42*, 3996–4028; b) G. Mehta, V. Singh, *Chem. Soc. Rev.* **2002**, *31*, 324–334; c) Y. Li, J. R. Dias, *Chem. Rev.* **1997**, *97*, 283–304.
[5] P. L. Toogood, *J. Med. Chem.* **2002**, *45*, 1543–1558.
[6] A. A. McCarthy, *Chem. Biol.* **2003**, *10*, 293–294.
[7] M. C. de la Torre, I. García, M. A. Sierra, *J. Org. Chem.* **2003**, *68*, 6611–6618.

[8] a) B. Rodríguez, G. Savona, F. Piozzi, *J. Org. Chem.* **1979**, *44*, 2219–2221; b) B. Rodriguez, G. Savona, *Magn. Reson. Chem.* **2000**, *38*, 802–804.

[9] L. J. Harrison, Y. Asakawa, *J. Chem. Res. Synop.* **1988**, 340–341. While this work was in progress a new hispanane named limbetazulone was isolated from *Ballota limbeta*, see: M. Riaz, K. Krohn, A. Malik, U. Flörke, *Chem. Biodiversity* **2004**, *1*, 458–462.

[10] a) M. C. de la Torre, I. García, M. A. Sierra, *J. Nat. Prod.* **2002**, *65*, 661–668; b) M. C. de la Torre, I. García, M. A. Sierra, *Tetrahedron Lett.* **2002**, *43*, 6351–6353.

[11] A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454–5459.

[12] Although strictly speaking labdanes are diterpenes isolated from natural sources, we have adopted for clarity and commodity the system numbering of the labdane diterpenoid backbone for the decaline framework of the compounds synthesized in this paper. See: J. D. Connoly, R. A. Hill, *Dictionary of Terpenoids*, *Vol. 1*, Chapman and Hall, London (UK), **1991**.

[13] A. F. Barrero, J. Altarejos, *Magn. Reson. Chem.* **1993**, *31*, 299–308.

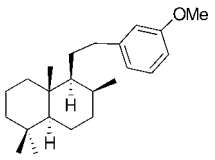
[14] a) A. J. Mancuso, S.-L. Huang, D. Swern, *J. Org. Chem.* **1978**, *43*, 2480–2482; b) A. J. Mancuso, D. S. Brownfain, D. Swern, *J. Org. Chem.* **1979**, *44*, 4148–4150; c) R. Ireland, D. Norbeck, *J. Org. Chem.* **1985**, *50*, 2198–2200.

[15] a) P. E. Eaton, G. R. Carlson, J. T. Lee, *J. Org. Chem.* **1973**, *38*, 4071–4073; b) M. Ueda, *Synlett* **1992**, 605–614; c) Y.-H. So, J. P. Heeschen, *J. Org. Chem.* **1997**, *62*, 3552–3561; d) N. Yonezawa, T. Hino, K. Matsuda, T. Matsuki, D. Narushima, M. Kobayashi, T. Ikeda, *J. Org. Chem.* **2000**, *65*, 941–944; e) L. W. McGarry, M. R. Detty, *J. Org. Chem.* **1990**, *55*, 4349–4356; f) V. Premasagar, V. A. Palaniswamy, E. J. Eisenbraun, *J. Org. Chem.* **1981**, *46*, 2974–2976; g) D. Zhao, D. L. Hughes, D. R. Bender, A. M. De Marco, P. J. Reider, *J. Org. Chem.* **1991**, *56*, 3001–3006.

[16] a) D. H. R. Barton, S. W. McCombie, *J. Chem. Soc. Perkin Trans. 1* **1975**, 1574–1585; b) D. H. R. Barton, W. B. Motherwell, A. Stange, *Synthesis* **1981**, 743–745; c) D. H. R. Barton, P. Blundell, J. Dorchak, D. O. Jang, J. C. Jaszberenyi, *Tetrahedron* **1991**, *47*, 8969–8984; d) D. H. R. Barton, W. Hartwig, R. S. Hay-Motherwell, W. B. Motherwell, A. Stange, *Tetrahedron Lett.* **1982**, *23*, 2019–2022; e) D. H. R. Barton, S. I. Parekh, Ch.-L. Tse, *Tetrahedron Lett.* **1993**, *34*, 2733–2736; f) Barton, D. H. R. *Tetrahedron* **1992**, *48*, 2529–2544; g) D. Crich, L. Quintero, *Chem. Rev.* **1989**, *89*, 1413–1432; h) W. B. Motherwell, D. Crich, *Free Radical Chain Reactions in Organic Synthesis*, Academic Press London, **1992**, pp. 47–50 and 54–58.

[17] For the mixture of alcohols **20e** and *epi*-**20e**, and also compound **22e**, epimeric thiols **23** and *epi*-**23** were obtained in 27% as by-products. Compounds **23** should be formed by a rearrangement of the firstly formed thioesthers followed by hydrolysis (Scheme 6). See: a) R. A. Batey, J. D. Harling, W. B. Motherwell, *Tetrahedron* **1992**, *48*, 8031–8052; b) K. Harano, S. Kiyonaga, S. Saimoro, T. Hirsano, *Heterocycles* **1988**, *27*, 2327–2330.

[18] The use of $BH_3{\cdot}SMe_2$ as the hydroborating agent for compound **22c** resulted in the formation of considerably amounts of C-17 β-methyl derivative **25c** together with the desired alcohol **24c**. This compound should be formed by a redox process between the intermediate trialkylorgano borane that is reduced by the SMe_2 that is oxidized to dimethyl sulfone, see: a) H. Weinheimer, J. Marisco, *J. Org. Chem.* **1962**, *27*, 1926–1926; b) H. C. Brown, A. K. Mandal, *J. Org. Chem.* **1980**, *45*, 916–917.



25c

[19] a) G. A. Kraus, M. J. Taschner, *J. Org. Chem.* **1980**, *45*, 1175–1176; b) G. A. Kraus, B. Roth, *J. Org. Chem.* **1980**, *45*, 4825–4830; c) B. S. Bal, W. E. Childers, H. W. Pinnik, *Tetrahedron* **1981**, *37*, 2091–2096.

[20] a) P. Dallemagne, S. Rault, J. C. Pilo, M. P. Foloppe, M. Robba, *Tetrahedron Lett.* **1991**, *32*, 6327–6328; b) Ch.-Y. Yick, T.-K. Tsang, H. N. C. Wong, *Tetrahedron* **2003**, *59*, 325–333.

[21] a) E. J. Corey, J. Das, *J. Am. Chem. Soc.* **1982**, *104*, 5551–5553, and references therein; b) P. A. Zoretic, R. J. Chambers, G. D. Marbury, A. A. Riebiro, *J. Org. Chem.* **1985**, *50*, 2981–2978; c) P. Magnus, T. Rainey, *Tetrahedron* **2001**, *57*, 8647–8651.

[22] S. Fueki, T. Tokiwano, H. Toshima, H. Oikawa, *Org. Lett.* **2004**, *6*, 2697–2700, and references therein.

Received: November 29, 2004
Published online: April 5, 2005

