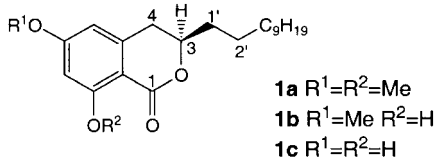
Stereoselective Synthesis of (3*R*)-3,4-Dihydro-6,8-dimethoxy-3-undecyl-1*H*-[2]benzopyran-1-one and Derivatives, Metabolites from *Ononis natrix*

by **Aamer Saeed**

Department of Chemistry, Quaid-I-Azam University, 45320-Islamabad, Pakistan
(e-mail: aamersaeed@yahoo.com)

A short stereoselective synthesis of (3*R*)-3,4-dihydro-6,8-dimethoxy-3-undecyl-1*H*-[2]benzopyran-1-one and derivatives isolated from *Ononis natrix* has been described. Condensation of dodecanoyl chloride with 3,5-dimethoxyhomophthalic acid afforded 6,8-dimethoxy-3-undecylisocoumarin **3**, which, on sequential saponification and esterification, yielded the keto ester **5**. Enantioselective reduction of **5** with TarB-NO_2/$LiBH_4$ directly furnished the title dihydroisocoumarin **1a** in 80% ee (82% yield). Partial as well as complete demethylation of the latter provided the dihydroisocoumarins **1b** and **1c**, respectively. Diastereotopy of the CH_2 H-atoms on either side of the stereogenic center (C(3)) and the mass-fragmentation pattern of the dihydroisocoumarins have also been described. All of the compounds synthesized were examined *in vitro* for antifungal activity.

Introduction. – *Ononis natrix* is a small flowering plant belonging to family Leguminosae. The infusion of its roots has diuretic, antirheumatic properties, and has been used for certain disturbances of the urinary tract. During phytochemical studies of this plant, *Feliciano et al.* had isolated 3,4-dihydro-6,8-dimethoxy-3-undecylisocoumarin (**1a**; $R^1 = R^2$=Me; isocoumarin = 1*H*-[2]benzopyran-1-one), its 8-hydroxy- (**1b**; R^1 = Me, R^2 = H) and 6,8-dihydroxy- (**1c**; $R^1 = R^2$ = H) derivatives as (*R*)-antipodes, from the hexane extract along with some related compounds [1][2]. *Kazlauskas et al.* had isolated earlier the related (3*R*)-3,4-dihydro-8-hydroxy-3-undecylisocoumarin from the brown alga *Caulocystis cephalornithos* [3].



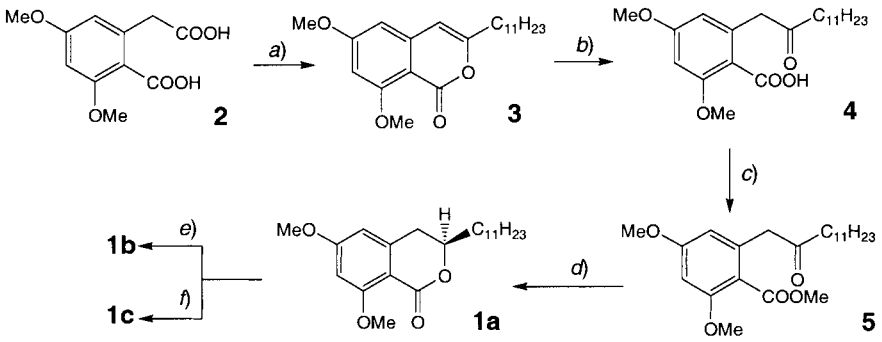
1a R^1=R^2=Me
1b R^1=Me R^2=H
1c R^1=R^2=H

We have already reported on the total synthesis of the title dihydroisocoumarins as racemates [4] by the multistep strategy developed during the synthesis of 6-methoxymellein, a phytoalexin, and metabolite of several fungi and peniolactol, the metabolite of the wood attacking fungus *Peniophora sanguinea* [5]. Title dihydroisocoumarins, besides their diuretic, antirheumatic, and antibacterial activities, are potential antifungal agents, and a detailed study of their biological profile required a short synthetic route. Condensation of acid chlorides with homophthalic acids has been useful for the construction of 3-substituted isocoumarin skeleton, which could easily be converted into corresponding 3,4-dihydroisocoumarins [6]. Herein, a facile stereo-

selective synthesis of title dihydroisocoumarins involving TarB-NO_2 as chiral *Lewis* acid for enantioselective reduction as a key step, and their antifungal activities are described.

Results and Discussion. – 3,5-Dimethoxyhomophthalic acid **2** was prepared from 3,5-dimethoxybenzyl bromide *via* Rh-catalyzed direct carbonylation to corresponding phenylacetic acid as a key step [7]. Direct condensation of 3,5-dimethoxyhomophthalic acid with dodecanoyl chloride at elevated temperature afforded the 6,8-dimethoxy-3-undecylisocoumarin **3** in 65% yield [8] (*Scheme 1*). It showed the characteristic 1-H *singlet* of isocoumarin moiety at δ 6.07 for H–C(4) in the ^{1}H-NMR and signals at δ 103.1 (C(4)) and 160.0 (C(3)) in the ^{13}C-NMR spectrum. DEPT 90° and DEPT 135° experiments confirmed these assignments. Mass spectrum showed the characteristic isocoumarin fragments at *m*/*z* 220, 205, and 177, in addition to the molecular ion, and IR spectrum showed the lactone C=O absorption at 1685 cm^{-1}.

Scheme 1



a) $C_{11}H_{23}COCl$, 200°, 4 h; 65%. *b*) 5% KOH, EtOH, 4 h reflux; 72%. *c*) MeI, K_2CO_3, dry acetone, 3 h; 95%. *d*) $LiBH_4$, TarB-NO_2, 2 h, r.t.; 82%. *e*) BBr_3, CH_2Cl_2, −78°, 10 min; 78%. *f*) BBr_3, CH_2Cl_2, −78° → r.t. overnight; 72%.

Alkaline hydrolysis of the isocoumarin **3** to furnish the 4,6-dimethoxy-2-(2-oxotridecyl)benzoic acid (**4**) was accomplished in 78% yield. The keto acid existed in equilibrium with its cyclic tautomeric lactol form *viz*. 3,4-dihydro-3-hydroxy-6,8-dimethoxy-3-undecylisocoumarin as evidenced by the ^{1}H-NMR. Thus, in addition to the 2-H singlet at δ 4.04 for benzylic H-atoms, (H–C(1′), open-chain form) each of the H-atoms showed a *triplet* at δ 2.57–2.61 (J = 4.2) and at 2.29–2.40 (J = 4.5) most probably by ^4J coupling in ^{1}H-NMR and signal for benzylic C-atom at δ 77.7 in ^{13}C-NMR spectrum was observed.

The keto acid was converted into the corresponding ester, as such keto esters are known to afford better enantioselectivities in stereoselective reductions. Esterification with absolute MeOH in presence of a catalytic amount of acid was unsuccessful and resulted in dehydration back to the parent isocoumarin. The esterification was successfully achieved by treatment with MeI in presence of anhydrous K_2CO_3 in dry acetone to afford the keto ester **5**. Keto ester **5** showed the 3-H *singlet* at 3.66 (COOMe) and 2-H *singlet* at 3.95 (ArCH_2) in ^{1}H-NMR, $[M - MeOH]^+$ ion at *m*/*z* 360

in MS, and ester and ketone C=O absorptions at 1716 and 1694 cm^{-1}, respectively, in IR spectrum.

The crucial step of the present synthesis was the enantioselective reduction of the prochiral keto acid **4** or keto ester **5**, for which the choice of a chiral reducing agent was important. The only precedence in literature of the stereoselective reduction of such keto acids or keto esters is by *Krohen et al.* [9]. Thus, reduction with *Midland*'s Alpine-boranes and enzymes like horse liver dehydrogenase were not successful, whereas more reactive diisopinocamphenyl boranes reduced the acid or ester to dihydroisocoumarin in 41 and 62% ee, respectively. Higher enantioselectivities were achieved with baker's yeast (> 99% ee) but with the opposite (*S*)-configuration. Other related examples include the CBS reduction of keto amides to amide alcohols in 15–45% ee (95% ee in one case), followed by basic hydrolysis to dihydroisocoumarins [10] and the DIBAL-H reduction of the chiral tricarbonyl complexes of prochiral ketones to homobenzylic alcohols as intermediates in the synthesis of dihydroisocoumarins, which gave good diastereoselection (75% de) [11]. We decided to use the recently reported tartaric acid derived boronate ester chiral *Lewis* acid, TarB-NO_2 in combination with $LiBH_4$ for enantioselective reduction of aryl ketones [12]. Thus, with 2 equiv. of TarB-NO_2 and 1 equiv. of $LiBH_4$ for 1 equiv. of keto ester **5**, the dihydroisocoumarin **1a** was obtained in 80% ee (82% yield) [13][14]. The enantiomeric excesses (ee) were determined by NMR with chiral shift reagents, and the absolute configuration was checked by the sign of optical rotation. The H-atoms of CH_2 groups on either side of the newly created stereogenic center (C(3)) exhibited the diastereotopic effect [15]. The $CH_2(4)$ with restricted motion owing to its incorporation in the heterocyclic ring, and $CH_2(1')$ and $CH_2(2')$ groups with free rotation correspond to *ABX*, *ABMNX*, and $ABMNX_2$ systems, respectively. The *AB* H-atoms ($CH_2(4)$) at δ 2.73–2.88 showed that the H-atom *cis* to side chain located slightly downfield shows a double *doublet* at δ 2.81–2.88 ppm ($J_{gem} = 16.4$, $J_{cis} = 3.5$ Hz), and the *trans*-H-atom resonates slightly upfield at 2.73–2.78 ppm ($J_{gem} = 16.2$, $J_{trans} = 11.9$ Hz), with a chemical shift difference of *ca.* 0.07 ppm, which corresponds to the extent of diastereotopy. The H–C(3) showed a *dddd* pattern at δ 4.31, indicating the presence of diastereotopic CH_2 groups on either side. Thus, each of the H-atoms of $CH_2(1')$ (H_A–C(1') and H_B–C(1')) also showed a *dddd* at δ 1.61 and 1.80 with a chemical shift difference of 0.19 ppm, an almost double extent of diastereotopy compared to that between H_A–C(4) and H_B–C(4). The diastereotopic effect extends up to the H-atoms of $CH_2(2')$ with two sets of *multiplets* at δ 1.45 and 1.54 ppm, respectively; in this case $\Delta\nu$ is reduced to *ca.* 0.1 ppm due to larger separation from the stereogenic center. There is no indication of diastereotopy beyond C(2'), and the rest of H-atoms ($CH_2(3')$–$CH_2(10')$) show an 18-H, br. *singlet* at δ 1.23 ppm. ^{13}C-NMR Spectrum showed signals at δ 77.6 and 35.0 for C(3) and C(4), respectively. The lactone C=O absorption appeared at 1720 cm^{-1} in IR spectrum.

Selective demethylation of the (3*R*)-3,4-dihydro-6,8-dimethoxy-3-undecylisocoumarin (**1a**) was carried out using BBr_3 under mild conditions (– 78°, 10 min) to furnish the (3*R*)-3,4-dihydro-8-hydroxy-6-methoxy-3-undecylisocoumarin (**1b**). ^{13}C-NMR Spectrum showed signals at δ 79.4 and 34.9 for C(3) and C(4), respectively. IR Spectrum showed the lactone C=O absorption at 1665 cm^{-1} due to internal chelation.

Complete demethylation of **1a** was achieved with BBr_3 at – 78° and allowing it to warm to 4° overnight to yield the (3*R*)-3,4-dihydro-6,8-dihydroxy-3-undecylisocou-

Table 1. *NMR Data for the H-Atoms at and around the Stereogenic Center* (C(3)) *of Dihydroisocoumarins* **1a**–**1c**

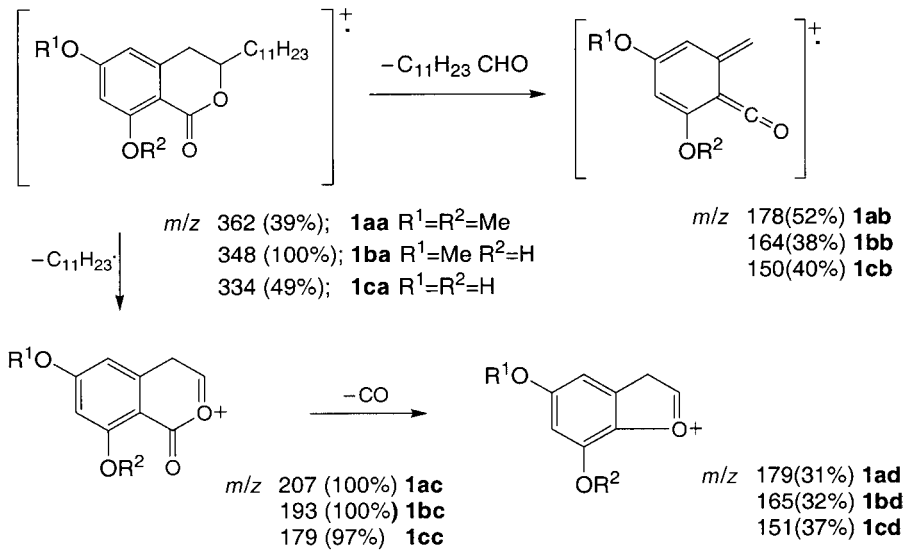
	H–C(3)	H_A–C(4)	H_B–C(4)	H_A–C(1′)	H_B–C(1′)	H_A–C(2′)	H_B–C(2′)
1a	4.31 (*dddd*, *J* = 10.5, 7.6, 5.4, 4.6)	2.85 (*dd*, *J* = 16.4, 3.52)	2.75 (*dd*, *J* = 16.2, 11.92)	1.61 (*dddd*, *J* = 13.5, 10.2, 5.7, 5.3)	1.80 (*dddd*, *J* = 13.7, 10.2, 7.4, 5.2)	1.40 (*m*)	1.54 (*m*)
1b	4.50 (*dddd*, *J* = 11.0, 7.5, 5.0, 3.7)	2.90 (*dd*, *J* = 16.5, 11.1)	2.83 (*dd*, *J* = 16.0, 3.7)	1.71 (*dddd*, *J* = 14.1, 10.4, 5.4, 5.3)	1.85 (*dddd*, *J* = 13.5, 10.3, 7.6, 5.4)	1.45 (*m*)	1.54 (*m*)
1c	4.70 (*dddd*, *J* = 11.2, 7.4, 5.5, 3.6)	2.96 (*dd*, *J* = 16.3, 4.0)	2.85 (*dd*, *J* = 16.2, 10.80)	1.75 (*dddd*, *J* = 14.0, 10.1, 7.5, 5.0)	1.89 (*dddd*, *J* = 13.6, 10.1, 7.4, 5.0)	1.47 (*m*)	1.60 (*m*)

marin (**1c**). The latter was characterized by the complete absence of MeO–C(8) and MeO–C(6) *singlets* both in ^{1}H- and ^{13}C-NMR spectra, and by the downfield shift of characteristic signals.

The NMR data for the H-atoms at and around the stereogenic center (C(3)) of the dihydroisocoumarins **1a**–**1c** are collected in *Table 1*. It is evident that the substituents R^1 and R^2 have no significant effect on splitting pattern and *J* values, except for slight variation of δ values. Thus, CH_2(4) H-atoms show a consistent J_{gem} value of 16.2 ± 0.3 Hz and two different J_{vic} values for *cis* and *trans* H-atoms with a ratio of *ca.* 1:3, the one resonating downfield and showing lower *J* value, but the order may be reversed. Similarly, the CH_2(1′) H-atoms couple to different extent with their vicinal counterparts.

Scheme 2 delineates the mass fragmentation pattern of the EI mass spectra of dihydroisocoumarins **1a**–**1c**, which is consistent with the general mass-fragmentation mechanism for dihydroisocoumarins. The major peaks correspond to α-cleavage, loss of CO, and *retro-Diels–Alder* cleavage products.

Scheme 2



The isocoumarin, keto acid, keto ester, and dihydroisocoumarin **3**, **4**, **5**, and **1a**–**1c**, respectively, were examined *in vitro* for antifungal activities against some human, animal, and plant pathogenic molds [16] (*Table 2*). It is evident from *Table 2* that **5** is more potent than **4**, and **1a** shows more antifungal activity compared to the corresponding isocoumarin **3**. Among dihydroisocoumarins **1a**–**1c**, 8-hydroxy and 6,8-dihydroxy derivatives, **1b** and **1c**, respectively, are more active compared to dimethoxy compound **1a**, possibly due to internal chelation between OH and lactone C=O groups [17].

Table 2. *Antifungal Activity* (antifungal activity determined by agar-dilution method and the results reported as linear-growth inhibition (LGI) [%] at 400 μg/ml [%] of media SDA; standard drugs: miconazole and ketoconazole)

Pathogens	**3**	**4**	**5**	**1a**	**1b**	**1c**	Standard drugs
Trichophyton schoenleinii	23	17.5	27	19.4	25.0	26.3	70
Candida albicans	–	–	–	–	–	–	79
Aspergillus niger	47.9	46.2	54	50	54	55	20
Microsporum canis	48.6	31	55	56	60	64	98.4
Fusarium solani	24.8	16.8	29.0	34	32	31	73.5
Pseudallescheria boydii	12.5	6.9	21	13.2	15	12.7	100

In summary, an efficient stereoselective synthesis of the principal dihydroisocoumarins of *Ononis natrix* has been accomplished. It involves three linear steps and proceeds with an overall yield of 40%.

Experimental Part

General. THF was dried over Na/benzophenone under N_2 and CH_2Cl_2 over CaH_2 under Ar and distilled fresh before use. Flash column chromatography (FC): *Merck Kieselgel 60* (230–400 mesh). Optical rotations: in $CHCl_3$ on a *Perkin-Elmer 341* polarimeter. IR Spectra were recorded on a *Bruker Vector 22*. ^{1}H- and the ^{13}C-NMR spectra were determined in $CDCl_3$ solns. at 400 (*Bruker AM-400*) and 100 MHz (*Bruker AM-100*), resp. EI-MS (70 eV): *MAT 312* instrument. Elemental analyses: *CHN-Rapid Heraeus*. Enantiomeric excesses (ee) were determined by ^{1}H-NMR with (+)-[Eu(hfc)$_3$] as optically active shift reagent.

*6,8-Dimethoxy-3-undecyl-1*H*-[2]benzopyran-1-one* (**3**). A stirred mixture of *3,5-dimethoxyhomophthalic acid* (**2**; 0.5 g, 2.08 mmol) and dodecanoyl chloride (1.82 g, 8.33 mmol) was heated on an oil bath at 200° for 4 h. FC of the residue (petroleum ether/AcOEt 9:2) afforded **3** (0.48 g, 1.35 mmol, 65%). Colorless prisms. IR (KBr): 2913, 2849, 1685, 1645, 1625, 1575, 1510, 860, 835, 810. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.87 (t, J = 7.12, Me(11′)); 1.25 (br. s, CH_2(3′) – CH_2(10′)); 1.65 (q, J = 8.4, CH_2(2′)); 2.44 (t, J = 7.0, CH_2(1′)); 3.87 (s, MeO–C(6)); 3.95 (s, MeO–C(8)); 6.07 (s, H–C(4)); 6.30 (s, H–C(5)); 6.41 (s, H–C(7)). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.5 (C(1)); 163.5 (C(8)); 160.0 (C(3)); 159.5 (C(6)); 142.6 (C(4a)); 103.1 (C(4)); 99.6 (C(5)); 98.3 (C(7)); 56.4 (*Me*O–C(8)); 55.7 (*Me*O–C(6)); 33.9 (C(1′)); 32.0 (C(9′)); 29.74, 29.72, 29.6, 29.55, 29.51, 29.4 (C(4′)–C(8′)); 26.9 (C(2′)); 24.7 (C(3′)); 22.8 (C(10′)); 14.2 (C(1′)). EI-MS (70 eV): 360 (63, M^+), 220 (43), 206 (17), 205 (100), 177 (52), 149 (38). Anal. calc. for $C_{22}H_{32}O_4$: C 73.30, H 8.95; found: C 73.21, H 8.98.

4,6-Dimethoxy-2-(2-oxotridecyl)benzoic Acid (or *3,4-Dihydro-3-hydroxy-6,8-dimethoxy-3-undecyl-1*H*-[2]benzopyran-1-one*; **4**). A stirred soln. of **3** (0.4 g, 1.11 mmol) in EtOH (15 ml) was treated with 5% KOH (30 ml), and the mixture was refluxed for 4 h. After cooling the mixture, most of the EtOH was evaporated. Cold H_2O (15 ml) was added, and the mixture was acidified with dil. HCl and extracted with AcOEt (2 × 30 ml). The org. phase was dried ($MgSO_4$), and the solvent was evaporated under vacuum to leave a solid.

Recrystallization from AcOEt/petroleum ether afforded **4** (0.30 g, 0.80 mmol, 72%). White scales. IR (KBr): 3011, 2949, 1716, 1683, 1601, 1202, 1162. ^{1}H-NMR (400 MHz, $CDCl_3$)[1]): 0.86 (*t*, *J* = 6.38, Me(11′)); 1.23 (br. *s*, CH_2(2′) – CH_2(10′)); 1.53 – 1.62 (*m*, CH_2(1′)); 2.29 – 2.40 (*t*, *J* = 4.5, 1 H–C(4)); 2.57 – 2.61 (*t*, *J* = 4.2, 1 H–C(4)); 3.84 (*s*, MeO); 3.98 (*s*, MeO); 6.39 (*d*, *J* = 2.0, H–C(7)); 6.47 (*d*, *J* = 2.2, H–C(5)); 11.22 (br. *s*, COOH). ^{13}C-NMR (100 MHz, $CDCl_3$): 195.5 (C(3), C=O); 168.3 (COOH); 132.7 (C(5)); 131.8 (C(6)); 127.4 (C(7)); 77.7 (C(4)); 55.6 (2 MeO); 42.9 (C(1′)); 32.1 (C(9′)); 29.8, 29.79, 29.77, 29.71, 29.68, 29.65, 29.6 (C(2′) – C(8′)); 22.8 (C(10′)); 14.2 (C(11′)). EI-MS: 378 (27.8, M^+), 360 (51), 220 (53), 195 (46), 178 (70), 150 (32). Anal. calc. for $C_{22}H_{34}O_5$: C 69.81, H 9.05; found: C 69.78, H 9.08.

Methyl 4,6-Dimethoxy-2-(2-oxotridecyl)benzoate (**5**). A mixture of **4** (0.25 g, 0.66 mmol) and anh. K_2CO_3 (0.5 g) in dry acetone (10 ml) was treated with MeI (56 mg, 24.7 ml, 0.78 mmol) and refluxed for 3 h. The mixture was filtered while hot, the filter cake was washed with warm dry acetone, and the solvent was evaporated to yield **5** (0.26 g, 0.66 mmol, 100%). Oil. IR (film): 3011, 2949, 1725, 1710, 1694, 1601, 1162. ^{1}H-NMR (400 MHz, $CDCl_3$; numbering according to cyclic form): 0.87 (*t*, *J* = 6.52, Me(11′)); 1.26 (br. *s*, CH_2(2′) – CH_2(10′)); 1.68 (*m*, CH_2(1′)); 2.27 – 2.35 (*t*, *J* = 4.2, 1 H–C(4)); 2.39 – 2.52 (*t*, *J* = 4.5, 1 H–C(4)); 3.66 (*s*, COOMe), 3.81 (*s*, MeO); 3.88 (*s*, MeO); 3.95 (*s*, ArCH_2); 6.30 (*d*, *J* = 2.0, H–C(7)); 6.41 (*d*, *J* = 2.24, H–C(5)). EI-MS: 392 (42.0, M^+), 237 (17.80), 220 (53), 209 (43.8), 178 (70). Anal. calc. for $C_{23}H_{36}O_5$: C 70.38, H 9.24; found: C 70.33, H 9.21.

*(3*R*)-3,4-Dihydro-6,8-dimethoxy-3-undecyl-1*H*-[2]benzopyran-1-one* (**1a**). A soln. of **5** (0.23 g, 0.6 mmol) in dry THF (40 ml) was added slowly *via* syringe to a stirred soln. of TarB-NO_2 (30 ml of 0.4M in THF, 0.12 mmol) under Ar. The mixture was stirred for 30 min at r.t. $LiBH_4$ (3 ml, 2M in THF, 0.6 mmol) was added dropwise over 10 min, and the mixture was further stirred for 2 h (TLC). The mixture was quenched with H_2O (5 ml), acidified with 2N HCl, and extracted with Et_2O (3 × 50 ml). The combined org. layer was washed with brine (30 ml), dried ($MgSO_4$), and concentrated. FC (petroleum ether/AcOEt 7:1) afforded **1a** (0.178 g, 0.49 mmol, 82%). Colorless scales. $[\alpha]_D^{25} = -59$ (*c* = 0.96, $CHCl_3$). IR (film): 2924, 2853, 1720, 1710, 1604, 1583, 1572, 1464, 1198, 832. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.86 (*t*, *J* = 6.0, Me(11′)); 1.23 (br. *s*, CH_2(2′) – CH_2(10′)); 1.40 (*m*, 1 H–C(2′)); 1.54 (*m*, 1 H–C(2′)); 1.61 (*dddd*, *J* = 13.5, 10.2, 5.7, 5.3, 1 H–C(1′)); 1.80 (*dddd*, *J* = 13.7, 10.2, 7.4, 5.2, 1 H–C(1′)); 2.73 – 2.75 (*dd*, J_{gem} = 16.2, J_{trans} = 11.92, 1 H–C(4)); 2.88 – 2.96 (*dd*, J_{gem} = 16.4, J_{cis} = 3.52, 1 H–C(4)); 3.85 (*s*, MeO–C(6)); 3.91 (*s*, MeO–C(8)); 4.28 – 4.31 (*dddd*, *J* = 10.5, 7.6, 5.4, 4.6, H–C(3)); 6.28 (*d*, *J* = 2.12, H–C(7)); 6.37 (*d*, *J* = 2.4, H–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 164.8 (C(1), CO); 163.0 (C(8)); 162.8 (C(6)); 144.0 (C(4a)); 107.2 (C(8a)); 103.9 (C(5)); 97.8 (C(7)); 77.6 (C(3)); 56.2 (*Me*O–C(8)); 55.6 (*Me*O–C(6)); 35.0 (C(4)); 34.8 (C(1′)); 32.0 (C(9′)); 29.74, 29.71, 29.68, 29.65, 29.6, 29.52, 29.5 (C(3′) – C(8′)); 25.0 (C(2′)); 22.8 (C(10′)); 14.2 (C(11′)). EI-MS (70 eV): 362 (39, M^+), 207 (100), 178 (52), 179 (31), 151 (42). Anal. calc. for $C_{22}H_{34}O_4$: C 72.85, H 9.45; found: C 72.81, H 9.44.

*(3*R*)-3,4-Dihydro-8-hydroxy-6-methoxy-3-undecyl-1*H*-[2]benzopyran-1-one* (**1b**). A 1M soln. of BBr_3 in CH_2Cl_2 (0.44 ml, 0.44 mmol) was injected to a stirred soln. of **1a** (80 mg, 0.22 mmol) in dry CH_2Cl_2 (3 ml) at –78°, under Ar. After stirring for 10 min, the mixture was poured into ice-water (20 ml) and stirred for 10 min. The layers were separated, and the aq. layer was extracted with CH_2Cl_2 (2 × 25 ml) and then with AcOEt (30 ml). The combined org. phases were dried ($MgSO_4$) and concentrated. FC (petroleum ether/AcOEt 8:2) afforded **1b** (60 mg, 0.17 mmol, 78%). Colorless prisms. $[\alpha]_D^{25} = -18.2$ (*c* = 0.31, $CHCl_3$). IR (film): 3435, 2956, 2924, 2855, 1727, 1665, 1627, 1461, 1461, 1271, 1249, 1121, 1072, 741. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.87 (*t*, *J* = 7.0, Me(11′)); 1.25 (br. *s*, CH_2(2′) – CH_2(10′)); 1.45 (*m*, 1 H–C(2′)); 1.55 (*m*, 1 H–C(2′)); 1.71 (*dddd*, *J* = 14.1, 10.4, 5.4, 5.3, 1 H–C(1′)); 1.85 (*dddd*, *J* = 13.5, 10.3, 7.6, 5.4, 1 H–C(1′)); 2.81 – 2.85 (*dd*, J_{gem} = 16.5, J_{cis} = 11.1, 1 H–C(4)); 2.84 – 2.96 (*dd*, J_{gem} = 16.0, J_{trans} = 3.7, 1 H–C(4)); 3.81 (*s*, MeO); 4.45 – 4.54 (*dddd*, *J* = 11.0, 7.5, 5.0, 3.7, H–C(3)); 6.24 (*d*, *J* = 2.76, H–C(7)); 6.36 (*d*, *J* = 2.64, H–C(5)); 11.25 (br., OH). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.0 (C(1), CO); 165.9 (C(6)); 164.7 (C(8)); 141.2 (C(4a)); 106.3 (C(5)); 103.9 (C(8a)); 99.5 (C(7)); 78.9 (C(3)); 55.6 (MeO); 34.9 (C(4)); 32.5 (C(1′)); 32.0 (C(9′)); 29.70, 29.69, 29.66, 29.64, 29.60, 29.54, 29.5 (C(3′) – C(8′)); 24.9 (C(2′)); 22.8 (C(10′)); 14.1 (C(11′)). EI-MS (70 eV): 348 (39, M^+), 207 (100), 178 (52), 179 (31), 151 (42). Anal. calc. for $C_{21}H_{32}O_4$: C 72.38, H 9.26; found: C 72.35, H 9.28.

*(3*R*)-3,4-Dihydro-6,8-dihydroxy-3-undecyl-1*H*-[2]benzopyran-1-one* (**1c**). A 1M soln. of BBr_3 in CH_2Cl_2 (0.88 ml, 0.88 mmol) was added dropwise to a stirred soln. of **1a** (80 mg, 0.22 mmol) in dry CH_2Cl_2 (3 ml) at –78° under Ar. The mixture was gradually allowed to warm to r.t. and stirred overnight. The mixture was poured into ice-cool H_2O, stirred for 10 min, and extracted with CH_2Cl_2 (3 × 30 ml) and then with AcOEt (30 ml). The combined org. phases were washed with H_2O, dried ($MgSO_4$), and concentrated. FC (petroleum

[1]) To avoid confusion and for direct comparison, C-atom numbering is considered same as in **3**.

ether/AcOEt 7:3) afforded **1c** (53 mg, 0.16 mmol, 72%). Colorless scales. $[\alpha]_D^{25} = -14.3$ ($c = 1.12$, $CHCl_3$). IR (film): 3435, 2956, 1727, 1669, 1627, 1461, 1461, 1271, 1249, 1121, 1072, 741. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.88 (t, $J = 6.5$, Me(11′)); 1.26 (br. s, $CH_2(2') - CH_2(10')$); 1.47 (m, 1 H–C(2′)); 1.60 (m, 1 H–C(2′)); 1.75 ($dddd$, $J =$ 14.0, 10.1, 7.5, 5.0, 1 H–C(1′)); 1.89 ($dddd$, $J = 13.6$, 10.1, 7.4, 5.0, 1 H–C(1′)); 2.81–2.85 (dd, $J_{gem} = 16.2$, $J_{trans} =$ 10.8, 1 H–C(4)); 2.84–2.96 (dd, $J_{gem} = 16.3$, $J_{trans} = 10.80$, 1 H–C(4)); 4.54–4.70 ($dddd$, $J = 10.5$, 7.6, 5.4, 4.6, H–C(3)); 6.24 (d, $J = 2.76$, H–C(7)); 6.36 (d, $J = 2.64$, H–C(5)). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.3 (C(1), CO); 164.9 (C(6)); 162.6 (C(8)); 142.0 (C(4a)); 106.9 (C(5)); 102.7 (C(8a)); 102.2 (C(7)); 79.9 (C(3)); 34.9 (C(4)); 33.2 (C(1′)); 32.0 (C(9′)); 29.73, 29.71, 29.67, 29.65, 29.60, 29.55, 29.52 (C(3′)–C(8′)); 24.9 (C(2′)); 22.6 (C(10′)); 14.2 (C(11′)). EI-MS (70 eV): 334 (49, M^+), 179 (97), 151 (37), 150 (40), 122 (34). Anal. calc. for $C_{20}H_{30}O_4$: C 71.82, H 9.04; found: C 71.86, H 9.01.

The author gratefully acknowledges a *Georg Forster* research fellowship from the *Alexander von Humboldt-Foundation* Germany. The author is indebted to the Instrumental Research Services, Institut für Organische Chemie, Universität Hannover, Germany, for the spectral analyses.

REFERENCES

[1] A. San Feliciano, A. F. Barrero, M. Medarde, J. M. Miguel del Corral, M. V. Calle, *Phytochemistry* **1983**, *22*, 2031.
[2] A. San Feliciano, J. M. Miguel del Corral, L. M. Canedo, M. Medarde, *Phytochemistry* **1990**, *29*, 945.
[3] R. Kazlauskas, J. Mulder, P. T. Murphy, R. J. Wells, *Aust. J. Chem*. **1980**, *33*, 2097.
[4] N. H. Rama, A. Saeed, C. W. Bird, *Liebigs Ann. Chem*. **1993**, 1331.
[5] N. H. Rama, A. Saeed, C. W. Bird, *Liebigs Ann. Chem*. **1995**, 711; N. H. Rama, R. Iqbal, A. Saeed, S. Hameed, *J. Chem. Soc. Pak*. **1992**, *14*. 138.
[6] A. Saeed, *Monatsh. Chem*. **2002**, in press; A. Saeed, *J. Chin. Chem. Soc.* **2002**, in press; N. H. Rama, R. Iqbal, Kh. Zamani, A. Saeed, M. Z. Iqbal, M. I. Chaudary, *Indian J. Chem*. **1998**, *37 B*, 365; A. Saeed, N. H. Rama, *Arabian J. Sci. Eng.* **1996**, *21*, 403.
[7] A. Giroux, C. Nadeau, Y. Han, *Tetrahedron Lett*. **2000**, *41*, 7601.
[8] K. Nozawa, M. Yamada, Y. Tsuda, K. I. Kawai, S. Nakajima, *Chem. Pharm. Bull.* **1981**, *29*, 2491, 3486; H. Kaji, M. Yamada, K. Nozawa, K. I. Kawai, S. Nakajima, *Org. Prep. Proced. Int*. **1986**, *18*, 253.
[9] K. Krohen, R. Bahramsari, U. Flörke, K. Ludewig, C. Nakajima, A. Klichespory, H.-J. Aust Michel, S. Raeger, B. Schulz, S. Antus, *Phytochemistry* **1997**, *45*, 313.
[10] A. Arnoldi, A. Bassoli, L. Merlini, E. Ragg, *Gazz. Chim. Ital*. **1992**, *122*, 403.
[11] R. Thangarasa, J. R. Green, T. Nadasdi, *J. Chem. Soc., Chem. Commun*. **1994**, 501.
[12] J. T. Suri, T. Vu, A. Hernandez, J. Congdon, B. Singaram, *Tetrahedron Lett*. **2002**, *43*, 3649.
[13] P. Bovicelli, P. Lupattelli, B. Crescenzi, A. Saetti, R. Bernini, *Tetrahedron* **1999**, *55*, 14719.
[14] K. Uchida, H. Watanabe, K. Mori, *Biosci. Biotech. Biochem*. **1997**, *61*, 1564.
[15] J. K. Kendall, T. H. Fisher, H. P. Schultz, T. P. Schultz, *J. Org. Chem*. **1989**, *54*, 4218.
[16] U. Kazmi, S. N. Ali, S. A. Jamal, A. Rehaman, *J. Pharm. Sci*. **1991**, *4*, 113; Atta-ur-Rahman, M. I. Choudhary, W. J. Thomsen in 'Bioassay Techniques for Drug Development', Harwood Academic Publishers, The Netherlands, 2001, p. 22.
[17] K. Nozawa, S. Nakajima, M. Yamada, K. I. Kawai, *Chem. Pharm. Bull*. **1980**, *28*, 1622.

Received July 23, 2002