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AN UNUSUAL CYCLOARTANE TRITERPENOID FROM *CIMICIFUGA FOETIDA*

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Key Word Index—*Cimicifuga foetida*; Ranunculaceae; cycloartane triterpenoid; neocimiside.

Abstract—A new cycloartane triterpenoid glycoside has been isolated from the rhizomes of *Cimicifuge foetida* L. The spectroscopic characteristics of the new compound are different from previously described cycloartane triterpenoids because of the loss of the 24-isopropyl group as well as the presence of a 11β-OH group. Based on spectroscopic evidence, including a series of 2D-NMR analyses, the structure of the new triterpene is assigned as 24-des-isopropyl-7-ene-23-one-9,19;16,24-dicycloart-3β,11β,16α,24α-tetraol 3-*O*-β-D-xylopryanoside, named here as neocimiside. The structure of the aglycone of neocimiside was confirmed by X-ray analysis.

INTRODUCTION

Members of the genus *Cimicifuga* (family Ranunculaceae) are widespread in China, and extracts of some species have been used to treat gynecological diseases [1]. High-performance TLC indicated that *C. foetida* rhizomes contain constituents similar to those reported for the European species *C. racemoca*, extracts of which are currently used as a clinical remedy to treat menopausal ailments (Remifemin®) (Schaper & Brummer, Salzgitter, Germany; Beuscher, N., personal communication). We previously reported new cycloartane triterpenoids [2–4], and other new compounds [5, 6], together with known compounds from *C. dahurica* and *C. foetida*. Here, we describe a new cycloartane triterpenoid, neocimiside (**1**). After this work was completed and submitted for publication, other workers confirmed structure **1** [7].

RESULTS AND DISCUSSION

Compound **1** was crystallized from methanol as small colourless needles which were, however, not suitable for X-ray analysis. Therefore, the structure assignment is based on both analytical data for the glycoside as well as X-ray analysis of the aglycone (**1a**). The composition of **1** was deduced to be $C_{32}H_{48}O_9$ from elemental analysis, FAB mass spectra and the ^1H and ^{13}C NMR data. Intense absorption bands at ν_{max} 3700–3000, 1722 and 1631 cm^{-1} in the IR spectrum of **1** was in accord with the presence of hydroxyl, carbonyl and olefinic functions, respectively. Chemical evidence and spectral data confirmed the presence of a β-D-xylopyranosyl moiety in **1**. The ^1H NMR spectrum of **1** showed four three-proton singlet signals for four tertiary methyl groups at δ 1.12, 1.23, 1.37 and 1.57 and a doublet ($J = 6.2$ Hz) for a single secondary methyl group at δ 0.88.

However, the structure could not be deduced from 1D-NMR data, therefore a series of 2D-NMR measurements were carried out, including ^1H–^1H COSY, ^{13}C–^1H COSY, ^1H–^1H TOCSY, ^{13}C–^1H COLOC and ^1H–^1H COSYLR. The 2D-NMR, together with mass spectral and IR data analyses, established the partial structures shown in Fig. 1.

The ^1H–^1H COSYLR experiment showed a small coupling cross-peak between the xylose anomeric proton (δ 4.84, 1H, *d*, $J = 7.3$ Hz) and the proton whose signal appeared at δ 3.56, thereby giving partial structure **a**. This finding indicated that the xylosyl group is attached to the carbon giving a ^{13}C NMR signal at δ 88.49. This result was confirmed by ^1H–^1H ROESY and NOE difference spectra, both of which showed NOE interactions between the two proton signals at δ 4.84 and 3.56. Calculation of the number of oxygen atoms and degrees of unsaturation suggested that the oxygen group on the carbon giving a signal at δ 63.61 (partial structure **b**) must be a hydroxyl group, and that the remaining two oxygen atoms must be adjacent hydroxyl functions connected to the two carbon atoms with signals at δ 82.03 and 82.37 as in partial structure **c**. This conclusion was confirmed by the NMR COLOC correlation between the signals at δ

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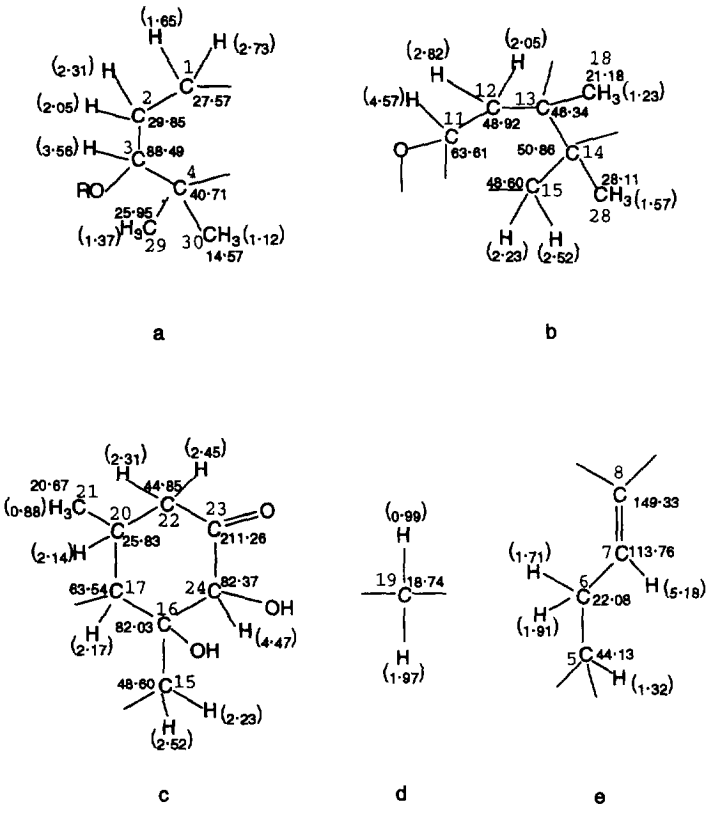

Fig. 1. Partial structural components of neocimiside (**1**) as deduced from NMR studies.

2.23 and 2.52 with the signal at δ 82.37, and by the correlation by COSYLR between signals at δ 4.47 and 2.17.

In the heteronuclear multiple bonds correlation spectrum, one of the methylene protons (partial structure **d**) with a signal at δ 0.99 exhibited cross-peaks with the carbon signals at δ 44.13 and 149.33; moreover, the geminal proton signal at δ 1.97 showed long-range correlations with the tertiary carbon signal at δ 29.17 as well as the methine carbon signal at δ 63.61. Moreover, both the two geminal ^{1}H signals at δ 0.99 and 1.97 demonstrated long-range polarization transfer to the carbon signal at δ 44.13, giving partial structure **e**. The COLOC correlation between the olefinic proton signal (5.18 ppm) and the methylene carbon signal at δ 27.54 indicated that there might be a tertiary carbon signal overlapped with the methylene carbon signal at δ 27.54 and, considering detectable heteronuclear polarization transfer, this tertiary carbon atom should be located two or three bonds distant from the olefinic proton. To confirm this deduction, a ^{13}C NMR spectrum was recorded with a larger acquisition number (NA = 32 000), on which the peak at δ 27.5 was enlarged, revealing two signals at δ 27.54 and 27.57. Thus, structure **1** (Fig. 2) was established for neocimiside, which is a new triterpenoid with the same fusion for rings A, B, C, D and E previously found for other cycloartanes from *C. foetida*. For detailed NMR correlations, see Tables 1 and 2.

Since the ^{13}C chemical shifts of the A-ring carbons of **1** are similar to those reported for cimigenol xyloside [2, 8], the xylosyl group is assigned a β-orientation, a conclusion supported by the cross-peaks between H-3 and H-5 on NOESY and ROESY. The NOE correlations between H-11 and H-28 on ROESY and NOE difference spectra confirmed a β-orientation of OH-11 in accord with the upfield shift of the signal for C-19 (δ 18.74), reflecting their adjacent relationship with the same orientation. This result is analogous to data for actein [8] and cimiside A [2], both of which exhibited C-18 signals shifted upfield *ca* 10 ppm as a result of a

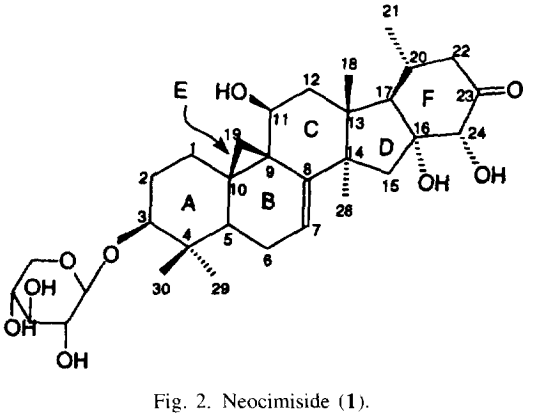

Fig. 2. Neocimiside (**1**).

Table 1. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectral data for compound **1**

Position	δ ^{13}C	δ ^{1}H, *m* (*J* in Hz)		^{1}H–^{13}C COLOC or HMBC correlation
1	27.57*	1α	1.65, *ddd* (13.9, 13.4, 2.4)	C-10
		1β	2.73 *ddd* (13.4, 4.4, 3.4)	
2	29.85	2α	2.31, *dd*-like†	
		2β	2.05, *dd*-like‡	
3	88.49	3α	3.56, *dd* (11.7, 4.0)	C-1′, C-4, C-29, C-30
4	40.71			
5	44.13	5α	1.32, *dd* (12.7, 5.2)	C-10, C-19
6	22.08	6α	1.91, *ddd* (16.5, 7.8, 5.2)	C-10
		6β	1.71, *ddd* (16.5, 12.7, 2.5)	
7	113.76		5.18, *dd* (7.8, 2.5)	C-5, C-9, C-14
8	149.33			
9	27.54*			
10	29.17			
11	63.61	11α	4.57, *dd* (9.7, 3.7)	
12	48.92	12α	2.82, *dd* (14.1, 9.7)	C-11, C-17
		12β	2.05, *dd*-like‡	C-11, C-14
13	46.34			
14	50.86			
15	48.60	15α	2.23, *d* (13.3)	C-8, C-13, C-14, C-16, C-24, C-28
		15β	2.52, *d* (13.3)	C-14, C-16, C-24
16	82.03			
17	63.54	17α	2.17, *d* (11.5)	C-16, C-18, C-24
18	21.18		1.23	C-12, C-13, C-14, C-17
19	18.74	19α	1.97, *d* (3.4)	C-5, C-10, C-11
		19β	0.99, *d* (3.4)	C-5, C-8
20	25.83	20β	2.14, *m*	
21	20.67		0.88, *d* (6.2)	
22	44.85	22α	2.45, *dd* (18.9, 12.7)	C-20
		22β	2.31, *dd*-like†	C-23
23	211.26			
24	82.37	24β	4.47, *s*	C-23
28	28.11		1.57, *s*	C-8, C-13, C-14, C-15
29	25.95		1.37, *s*	C-3, C-4, C-5, C-30
30	14.57		1.12, *s*	C-3, C-4, C-5, C-29
Xyl-1′	107.44	1′	4.84, *d* (7.3)	C-3
2′	75.53	2′	4.01, *t* (8.1)	
3′	78.55	3′	4.15, *t* (8.7)	
4′	71.22	4′	4.18, *m*	
5′	67.07	5′	3.71, *t* (10.6)	
			4.31, *dd* (11.4, 5.1)	

Solvent: pyridine-d_5, coupling constants (*J*) were observed by *J*-resolved ^{1}H NMR spectra.
*Signals may be interchanged.
†, ‡Overlapped signals.

12β oxygen group; moreover, 7β-hydroxy-23-*O*-acetylshengmanol 3-*O*-β-D-xylopyranoside [9] and cimiside C [3], both of which exhibited the C-28 signals to shift upfield *ca* 10 ppm, as a result of C-15α oxygen functionalities. Furthermore, the protons on C-19 for **1** sharply shifted downfield, and appeared at δ 0.99 and 1.97, respectively. The cross-peak between H-19 (δ 0.99) and H-1α (δ 1.65) on COSYLR inferred a 'W' type long-range coupling between one H-19 and H-1α; moreover, the other H-19 (δ 1.97) showed NOE interaction on ROESY with H-1β (δ 2.73). This evidence supported the β-configuration of the cyclopropane ring.

In ROESY and NOE difference experiments, H-20 exhibited NOE correlations, respectively, with H-18 and H-24; in addition, there was also an NOE correlation between H-18 and H-24. These findings not only confirmed an α-orientation for the 21-methyl, but indicated an α-orientation of the 24-hydroxyl; nevertheless, the orientation of the 16-hydroxy group was still ambiguous. Based on all the correlations observed with the 2D-NMR studies and NOE difference spectra, we could assign all proton and carbon signals for **1** (see Table 1).

Hydrolysis of **1** by cellulase afforded an aglycone (**1a**), which was subjected to X-ray analysis using a single crystal of dimensions $0.150 \times 0.150 \times 0.500$ mm crystallizing in the monoclinic space group $P2_1$ with $a = 9.432(4)$, $b = 6.508(5)$, $c = 19.046(2)$ Å, $\beta = 92.96(2)°$, $V = 1168(1)$ Å^3, $Z = 2$, $D_c = 1.265$ g cm^{-3}, $R = 0.066$ for 5566 independent reflections. Data were corrected for absorption and secondary extinction. The

Table 2. Homonuclear long-range correlations observed for compound **1**

Proton	COSYLR	ROESY
H-1α	H-19β, H-1β	H-1β, H-3α, H-11α,
H-1β	H-1α	H-1α, H-19α
H-2α	H-3α	H-2β, H-3α
H-2β		H-2α
H-3α	H-1′, H-2α, H-30	H-1α, H-2α, H-5, H-1′
H-5	H-6α, H-30	H-3α, H-1′
H-6α	H-5	H-7
H-6β	H-7	
H-7	H-6β	H-6α, H-15α, H-15β
H-11α	H-12α	H-1α, H-12α, H-28
H-12α	H-11α, H-18	H-12β, H-11α, H-17
H-12β		H-12α, H-18
H-15α	H-15β	H-7, H-15β
H-15β	H-15α, H-28	H-7, H-15α, H-24
H-17	H-18	H-12α, H-28
H-18	H-12α, H-17, H-28	H-12β, H-20, H-24
H-19α		H-1β, H-19β
H-19β	H-1α	H-19α
H-20	H-21, H-22α	H-18, H-21, H-24
H-21	H-20, H-22α	H-20
H-22α	H-21	
H-22β	H-24	
H-24	H-20, H-22β	H-15β, H-18, H-20
H-28	H-15β	H-11α, H-17
H-29	H-30	
H-30	H-3α, H-5α, H-29	
H-1′	H-3α	H-3α, H-5α

structure of the aglycone (Fig. 3) was solved by direct methods, and the largest peaks in the final difference map were 0.28 and -0.27 eÅ^{-3}. The backbone of this triterpenoid molecule consists of four six-membered rings, a five-membered ring and a three-membered ring. One six-membered ring (C-1–C-2–C-3–C-4–C-5–C-10) is in the chair conformation, one (C-16–C-17–C-20–C-22–C-23–C-24) exhibits a boat conformation and the remaining two rings assume a conformation resembling a skew-boat. The five-membered ring exhibits a slightly distorted envelope conformation. All rings are *trans* fused except for rings D (C-13–C-17) and E (C-16–C-24) which are *cis* fused. The methyl groups at C-13 and C-14 are in an axial position. The methyl group at C-20 is equatorial, as are the two hydroxyl groups at C-3 and C-24. The third hydroxyl group at C-16 is in an axial orientation, while the fourth hydroxyl group at C-11 has a bisectional orientation. The two hydroxyl groups at C-16 and C-24 are *cis* to each other.

An interesting hydrogen bond pattern was detected in the crystal structure of the investigated compound. There is an intramolecular hydrogen bond between the hydrogen atom from one of the hydroxyl groups (H-5) and the carbonyl oxygen atom (O-4). Two intermolecular hydrogen bonds were also located in the structure. One occurs between the hydrogen atom of the bisectionally oriented hydroxyl group (H-2) and the O-1 atom from an adjacent molecule. The other intermolecular hydrogen bond is formed between H-3 from the axially oriented hydroxyl group at C-16 and an O-5 from another neighbouring molecule. The geometric data of the three hydrogen bonds are summarized in Table 3. This X-ray analysis not only confirmed the previously deduced structure of **1**, but established an α-orientation of the 16-hydroxyl group and the *cis*-fused D/F rings.

EXPERIMENTAL

General experimental procedures. 1D- and 2D-NMR spectra were recorded on a Bruker AM-500, and chemical shifts are reported in ppm using the solvent as reference. The optical rotation was determined on a Perkin-Elmer 241 polarimeter. The IR spectrum was recorded on a Perkin-Elmer 983 spectrometer. FAB-MS

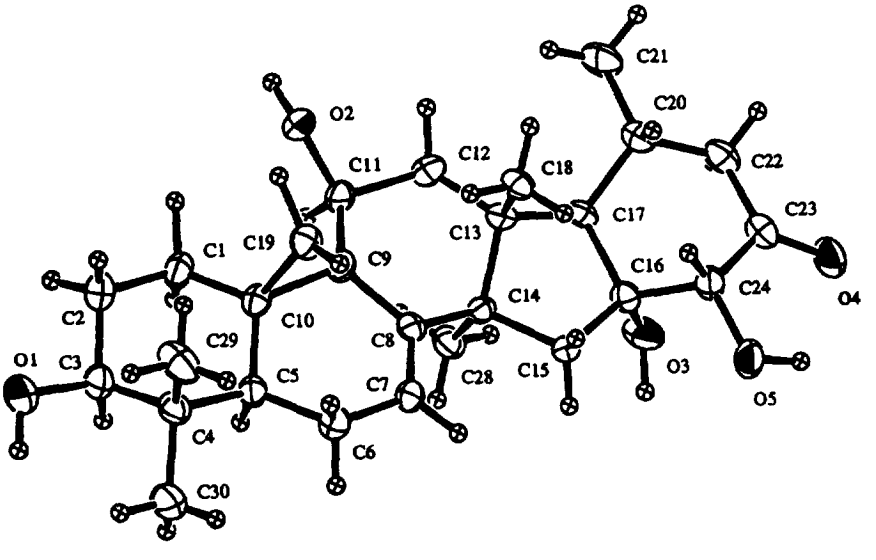

Fig. 3. Stereoscopic view of the aglycone (**1a**).

Table 3. Hydrogen bonding in compound **1a**

Donor---H...acceptor	Acceptor atom coordinates	D...A (Å)	H...A (Å)	D---H...A (°)
O5---H5...O4	x, y, z	2.635 (6)	2.09	115.1
O2---H2...O1	$2-x, y^{+1/2}, -z$	2.924 (5)	1.95	173
O3---H3...O5	$2-x, y^{+1/2}, 1-z$	2.837 (5)	2.04	140.5

were performed on a Finnigan MAT 90 mass spectrometer.

Plant material. Rhizomes of *C. foetida* were collected by Dr S.-X. Guo (IMPLAD, Beijing, China) in August, 1992, in the Lin-fen District, Shanxi Province, China. The material was identified by Prof. Xiao Peigen, and a voucher specimen is deposited in the Institute of Medicinal Plant Development (IMPLAD), Chinese Academy of Medical Sciences, Beijing.

Extraction and isolation. Dried rhizome material of *C. foetida* (30 kg) was ground to a powder, which was extracted with EtOH. The concentrate from the extract was treated with H_2O at 50–60° and the resulting mixt. was filtered. The H_2O-insoluble material (162 g) was dissolved in CH_2Cl_2, and the resulting soln was subjected to silica gel CC using $CHCl_3$ containing increasing amounts of MeOH as eluent, up to $CHCl_3$–MeOH (5:1), to yield 4.5 g of material. This crude material was rechromatographed over silica gel using EtOAc as eluent; frs of 200 ml each were collected. The concentrate from frs 3–5 was dissolved in $CHCl_3$–MeOH (1:1) and passed over an alumina column to remove pigments; the resulting material was then further purified over a Sephadex LH-20 column eluted with MeOH. Recrystallization from MeOH of the residue gave 230 mg pure material.

Neocimiside (**1**). Needles, mp 260–262° (MeOH); IR ν_{max} 3700–3000, 2927, 2852, 1722, 1631, 1460, 1400, 1380, 1284, 1160, 1073, 1044, 900, 815 cm^{-1}. Elemental analysis (%): C, 66.64; H, 8.38, calc. for $C_{32}H_{48}O_9$, C, 66.67: H, 8.33. FAB-MS: $[M+1]^+$ 577, $[(M+1)-18]^+$ 559; HR-FABMS: $[M+1]^+$ 577.3366, calc. for $C_{32}H_{49}O_9$: 577.3376. $[\alpha]_D$ −76.2° [*c* 0.63, $CHCl_3$–MeOH (1:1)]; for ^1H NMR (pyridine-d_5 500 MHz) and ^{13}C NMR (pyridine-d_5, 125 MHz); for data see Table 1.

Hydrolysis of **1** *with cellulase.* Compound **1** (53 mg) was dissolved in MeOH (10 ml) and water (20 ml) was added. A soln of Cellulast (a commercial prepn of cellulase from *Trichodesma reese*, Novo Nordisk, Denmark) was added dropwise and the mixt. was kept at 25° in an incubator for 1 week. The reaction soln was extracted with EtOAc (20 ml × 3) and the EtOAc layer washed with H_2O (10 ml × 3). After evapn of the solvent *in vacuo*, the residue was subjected to CC on silica gel. Elution with *n*-hexane–EtOAc (1:1) afforded an aglycone (**1a**, 30 mg), which was recrystallized in EtOAc for X-ray assay: mp 209–211°; HR-EIMS *m/z* 444.2877 $[M]^+$, calc. for $C_{27}H_{40}O_5$: 444.2875; $[\alpha]_D$ −34.5° (*c* 0.49, Me_2CO).

X-Ray analysis of **1a**. Summary of experimental details of X-ray diffraction analysis of **1a**: see Table 4. A parallelepiped crystal of $C_{27}H_{40}O_5$ having dimensions of *ca* 0.15 × 0.15 × 0.5 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu K_α radiation. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement of the setting angles of 21 centred reflections in the range $51.34° < 2\theta < 76.80°$. The data were collected at room temp. (298±2 K) using the ω–2θ scan mode to a max. 2θ value of 158.1°. Scans of $(1.73 + 0.30 \tan\theta)°$ were made at 8.0° min^{-1} (in ω). The weak reflections $[I < 10.0\sigma(I)]$ were rescanned (up to ×3) and the counts were accumulated to ensure reliable counting statistics. Of the 5566 reflections collected, 2629 were unique ($R_{int} = 0.030$). The intensities of 3 reflections (1 −2 2; 1 −1 3; 2 −1 −2), which were measured after every 150 reflections, remained constant throughout data collection, indicating crystal and electronic stability (no decay correction was necessary). An empirical absorption correction based on azimuthal scans of 3 reflections was applied. The resulting transmission factors ranged from 0.68 to 1.00. The data were corrected for Lorentz and polarization effects as well as for secondary extinction (coefficient = 0.10173E − 05).

The structure was solved using direct methods (SHELXS-86) [10]. The non-H atoms were refined with anisotropic displacement parameters by full-matrix least-square procedure (TEXSAN) [11] based on 4231 observed reflections $[I > 3.00\sigma(I)]$ and 357 variable parameters. The H atoms were included in the difference Fourier map locations or at calculated positions with isotropic displacement parameters estimated from the displacement parameter of the adjacent carbon atom. The refinement converged (largest parameter shift was 0.15σ) with unweighted and weighted agreement indices of $R = \sum ||F_o| - |F_c|| / \sum |F_o| = 0.066$ and $R_w = [(\sum w(|F_o| - |F_c|)^2 / \sum wF_o^2)]^{1/2} = 0.065$ ($w = 4F_o^2 O^2(F_o^2)$). Goodness of fit $S = [\sum w(|F_o| - |F_c|)^2 / (N_o - N_v)]^{1/2} = 3.36$ of F values for 357 parameters. Neutral atoms scattering factors are from Cromer and Waber [12]. Anomalous dispersion effects were included in calculated structure factors [13], the values for Δf and $\Delta f'$ were those of Cromer [14]. The absolute configuration could not be determined. Programs used in calculation include: SHELXS-86 [10], TEXSAN [11], PLATON [15] and for molecular graphics ORTEP [16]. Tables of atomic coordinates, displacement parameters, bond lengths and angles as well as structure factors for **1a** are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Cambridge, U.K.

Table 4. Crystallographic data and data collection characteristics for the X-Ray analysis of compound **1a**

Crystal data		
Molecular formula	$C_{27}H_{40}O_5$	
M_r	444.61	
Crystal system	Monoclinic	
Space group	$P2_1$	
Cell dimensions (nm) a	0.9432(4)	$\alpha = 90°$
b	0.6508(5)	$\beta = 92.96(2)°$
c	1.9046(2)	$\gamma = 90°$
Volume (nm^3)	1.168(1)	
Z	2	
Density (mg m^{-3})	1.265	
Absorption coefficient (mm^{-1})	0.645	
$F(000)$	484	
Crystal size (nm)	$0.15 \times 0.15 \times 0.5$	
Data collection: Rigaku AFC6S; graphite monochromated Cu K_α		
Temperature (K)	298	
ω–2θ scans	($3° < 2\theta < 158°$)	
Reflections collected	5566	
Independent reflections	2629 ($R_{int} = 0.030$)	
Observed reflections	4231 ($I > 3\sigma(I)$)	
Parameters refined	357	
Final R; R_w	0.066; 0.065	
Goodness of fit	3.36	

Acknowledgements—We are grateful to Mr Guang-zhong Tu in The Beijing Institute of Microchemistry for measuring all 1D- and 2D-NMR spectra and for helpful discussions. This investigation was supported by the Doctoral Program, State Education Commission of China and funds from the Graduate School, Chinese Academy of Medical Sciences and Peking Union Medical College. Work at The University of Texas at Austin was supported by the National Institutes of Health (GM-35710) and the Robert A. Welch Foundation (Grant F-130).

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