Two New Sesquiterpenes from *Euonymus alatus*

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Two new sesquiterpenes, **1** and **2**, as well as the five known compounds **3**–**7**, were isolated from the stems of *Euonymus alatus*. Compounds **2**–**7** have a β-dihydroagarofuran skeleton. The structures of these compounds were elucidated mainly by spectroscopic methods (1D-, 2D-NMR, ESI-MS, and HR-ESI-MS). We also report the X-ray crystal structure of evonine (**3**) for the first time.

Introduction. – The Celastraceae, which contain about 98 genus and 1210 species [1], produce various β-dihydroagarofuran sesquiterpene polyol esters and alkaloids [2]. All these constituents belong to the eudesmane sesquiterpene family. Meanwhile, these kinds of compounds have also been isolated from the plants of the genus *Euonymus* [3–10]. *Euonymus alatus*, known as winged euonymus or 'Gui Jian Yu' in China in the genus *Euonymus*, has been used as a folk medicine for over 2000 years [11] and is widely used for the therapy of tumors, diabetes, and wound [12–16]. So far, several kinds of compounds have been isolated from this plant, including cardenolides, flavonoids, steroids, triterpenes, and sesquiterpenes [14][16–21]. Our phytochemical studies led to the isolation of the two new sesquiterpenes **1** and **2**, along with five known ones, **3**–**7**, from the 95% EtOH extract of the stems of *Euonymus alatus*. We also report here the X-ray crystal structure of evonine (**3**) for the first time.

Results and Discussion. – The 95% EtOH extract of the stems of *E. alatus* was partitioned into fractions soluble in petroleum ether and AcOEt. Repeated column chromatography over silica gel (SiO_2), *Sephadex LH-20*, and *ODS* of the petroleum ether fraction led to seven compounds, *i.e.*, the two new sesquiterpenes **1** and **2** (*Fig. 1*), along with five known ones evonine (**3**), neoevonine (**4**), 1β,2β,5α,8β,11-pentaacetoxy-4α-hydroxy-3α-(2-methylbutanoyl)-15-nicotinoyl-7-oxo-dihydroagarofuran (**5**), 6α,12-diacetoxy-2β,9α-di(β-furancarbonyloxy)-4α-hydroxy-1β-(2-methylbutanoyloxy)-β-dihydroagarofuran (**6**), 1α,2α,6β-triacetoxy-4β-hydroxy-9β-(β-)furancarboxy-15-[(α-methyl)butyroyloxy]-β-dihydroagarofuran (**7**).

Compound **1**[1]), a colorless oil, showed the $[M+Na]^+$ ion at *m/z* 361.2345 in its HR-ESI-MS, suggesting the molecular formula $C_{20}H_{34}O_4$ and the presence of 4 degrees of

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[1]) Trivial atom numbering; for systematic names of **1** and **2**, see *Exper. Part.*

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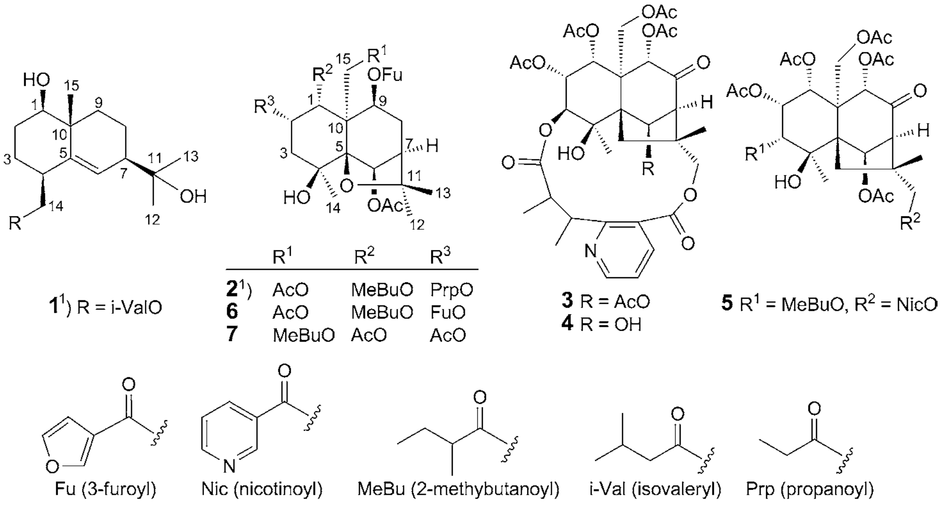

Fig. 1. *Compounds* **1**–**7**, *isolated from* Euonymus alatus

unsaturation. The IR spectrum showed OH-type absorption bands at 3436 cm^{-1} and ester-carbonyl bands at 1733 cm^{-1}. The ^1H-NMR spectrum (*Table 1*) revealed two *d*s at δ(H) 0.92 (J = 6.8 Hz, 6 H) and 2.15 (J = 6.4 Hz, 2 H) and one *m* at δ(H) 2.01–2.06 (overlapped, 1 H), consistent with the presence of an isovaleryloxy (= 3-methyl-1-oxobutoxy) unit. Moreover, the ^1H-NMR spectrum showed three Me *s* at δ(H) 0.96, 1.11, and 1.13, one CH_2 group at δ(H) 3.98 (*dd*, J = 6.8, 10.8 Hz, 1 H) and 4.23 (*dd*, J = 9.2, 10.8 Hz, 1 H), and the H-atom of a trisubstituted double bond at δ(H) 5.66 (*d*, J = 2.8 Hz, 1 H), the latter being also suggested by the ^{13}C-NMR signals (*Table 1*) at δ(C) 144.37 (*s*) and 129.24 (*d*). The HSQC and COSY data (*Table 1* and *Fig. 2*) established the fragments $CH(1)CH_2(2)CH_2(3)CH(4)CH_2(14)$ and $CH(6)CH(7)CH_2(8)CH_2(9)$. The HMBC experiment (*Fig. 2*) and all the above data presented the skeleton fragment correlation from C(1) to C(10). In the HMBC spectrum, the cross-peaks δ(H) 0.96 (*s*, Me(15))/δ(C) 78.22 (C(1)), 35.99 (C(9)), and 41.12 (C(10)), δ(H) 1.11 (*s*, Me(12)) and 1.13 (*s*, Me(13))/δ(C) 74.03 (C(11)) and 47.36 (C(7)), as well as δ(H) 3.98 and 4.23 (2*dd*, $CH_2(14)$/δ(C) 174.95 (C=O of isovaleryloxy) were present. Moreover, the molecular mass and the ^1H- and ^{13}C-NMR data indicated that C(1) (δ(C) 78.22) and C(11) (δ(C) 74.03) should be substituted by OH groups. In the NOESY experiment (*Fig. 3*), H–C(1) (δ(H) 3.25–3.29) showed a correlation with H–C(4) (δ(H) 2.49–2.54); thus both H-atoms were arbitrarily assigned as being on the α-side. The NOE correlation Me(15) (δ(H) 0.96)/$CH_2(14)$ (δ(H) 3.98 and 4.23) and the absence of a correlation Me(15)/H–C(1) indicated that Me(15) and C(14) were on the β-side. The NOEs H_α–C(9) (δ(H) 1.65–1.67)/H–C(1) and H–C(7) (δ(H) 2.01–2.06) showed that H–C(7) was on the α-side. Thus the relative configuration of **1** was determined. All the above data and comparison with those given in [22] established the structure of **1**.

Compound **2**[1]) was obtained as a white powder. Its molecular formula $C_{32}H_{44}O_{13}$ was deduced from the HR-ESI-MS (*m/z* 659.2706 ($[M + Na]^+$), indicating the presence of 11 degrees of unsaturation. The IR spectrum showed an OH-type absorption band at

Table 1. *^{1}H- and ^{13}C-NMR Data* (400 and 100 MHz, resp.; CD_3OD) *of* **1**[1]). δ in ppm, *J* in Hz.

Position	δ(H)	δ(C)	^{1}H,^{1}H-COSY
H–C(1)	3.25–3.29 (*m*, overlapped)	78.2 (*d*)	H–C(2)
CH_2(2)	1.56–1.61 (*m*)	27.5 (*t*)	H–C(1), H$_{\text{a and b}}$–C(3)
CH_2(3)	1.70–1.75 (*m*, H$_a$), 1.48–1.51 (*m*, H$_b$)	27.1 (*t*)	H–C(2), H$_b$–C(3), H–C(4) H–C(2), H$_a$–C(3), H–C(4)
H–C(4)	2.49–2.54 (*m*)	45.1 (*d*)	H$_{\text{a and b}}$–C(3), H$_{\text{a and b}}$–C(14)
C(5)		144.3 (*s*)	
H–C(6)	5.66 (*d*, *J* = 2.8)	129.2 (*d*)	H–C(7)
H–C(7)	2.01–2.06 (*m*, overlapped)	47.3 (*d*)	H–C(6), H$_{\alpha \text{ and } \beta}$–C(8)
CH_2(8)	1.54–1.56 (*m*, H$_\alpha$), 1.62–1.64 (*m*, H$_\beta$)	21.2 (*t*)	H–C(7), H$_\beta$–C(8), H$_{\alpha \text{ and } \beta}$–C(9) H–C(7), H$_\alpha$–C(8), H$_{\alpha \text{ and } \beta}$–C(9)
CH_2(9)	1.65–1.67 (*m*, H$_\alpha$), 1.45–1.47 (*m*, H$_\beta$)	35.9 (*t*)	H$_{\alpha \text{ and } \beta}$–C(8), H$_\beta$–C(9) H$_{\alpha \text{ and } \beta}$–C(8), H$_\alpha$–C(9)
C(10)		41.1 (*s*)	
C(11)		74.0 (*s*)	
Me(12)	1.11 (*s*)	27.2 (*q*)	
Me(13)	1.13 (*s*)	27.5 (*q*)	
CH_2(14)	4.23 (*dd*, *J* = 9.2, 10.8, H$_a$), 3.98 (*dd*, *J* = 6.8, 10.8, H$_b$)	67.8 (*t*)	H–C(4), H$_b$–C(14) H–C(4), H$_a$–C(14)
Me(15)	0.96 (*s*)	21.0 (*q*)	
i-ValO		174.9 (*s*)	
	2.15 (*d*, *J* = 6.4)	44.5 (*t*)	
	2.01–2.06 (*m*, overlapped)	27.0 (*d*)	
	0.92 (*d*, *J* = 6.8)	22.9 (*q*)	
	0.92 (*d*, *J* = 6.8)	22.9 (*q*)	

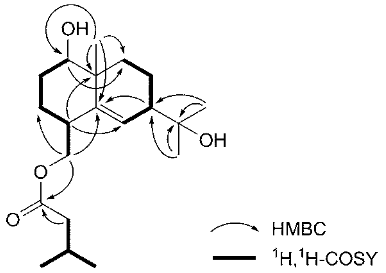

Fig. 2. *Selected 2D-NMR correlations of* **1**

3445 cm^{-1} and ester-carbonyl bands at 1749 and 1718 cm^{-1}. The ^{1}H-NMR spectrum (*Table 2*) exhibited a *s* (δ(H) 7.97 (1 H)) and two *d* (δ(H) 6.68 (*d*, *J* = 1.0 Hz, 1 H) and 7.37 (*d*, *J* = 1.0 Hz, 1 H)), which were attributed to a (furylcarbonyl)oxy substituent. A *t* (δ(H) 0.63 (*J* = 7.5 Hz, 3 H)), a *d* (δ(H) 0.84 (*J* = 7.5 Hz, 3 H)), and three *m* (δ(H) 1.91–1.97, 1.24–1.32, and 0.98–1.07 (1 H each)) were attributed to a (2-methylbutanoyl)oxy substituent, and a *t* (δ(H) 1.12 (*J* = 7.5 Hz, 3 H)) and a *q* (δ(H) 2.33 (*J* = 7.5 Hz, 2 H)) to a propanoyloxy moiety. All these data were certified by the ^{13}C-NMR spectrum (*Table 2*). Moreover, the ^{1}H-NMR spectrum contained signals assignable to four CH groups carrying an ester group at δ(H) 6.07 (*s*, H–C(6)), 5.54 (*d*, *J* = 3.0 Hz, H–C(1)), 5.45–5.47 (*m*, H–C(2)), and 5.17 (*d*, *J* = 7.0 Hz, H–C(9)), to a

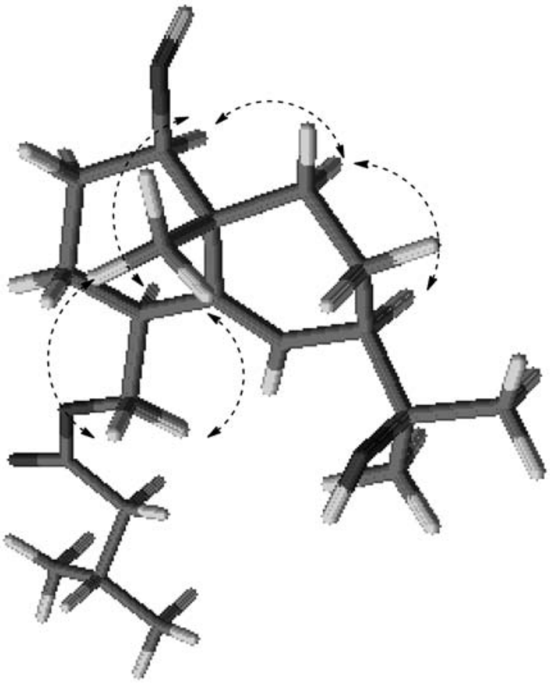

Fig. 3. *Key NOESY correlations of* **1**

CH_2 group carrying an ester group at δ(H) 4.35 and 4.95 (*AB*, *J* = 13.0 Hz, $CH_2(15)$), to a tertiary Me group at δ(H) 1.41 (*s*, Me(14)) attached to a C-Atom at δ(C) 69.80 (C(4)) carrying an OH group, to two acetate Me groups at δ(H) 2.07 and 2.22 (2*s*), and to two tertiary Me groups at δ(H) 1.43 (*s*, Me(12)) and 1.50 (*s*, Me(13)). All the above data and 2D-NMR experiments (HSQC and COSY (*Fig. 4*)) indicated that **2** was a β-dihydroagarofuran sesquiterpene with one (furylcarbonyl)oxy, one (2-methylbutanoyl)oxy, one propanoyloxy, and two acetoxy groups. The positions of these substituent groups were deduced from the HMBC data (*Fig. 4*), which showed the correlations H–C(1) (δ(H) 5.54/δ(C) 174.54 (C=O of MeBuO), H–C(2) (δ(H) 5.45–5.47)/δ(C)

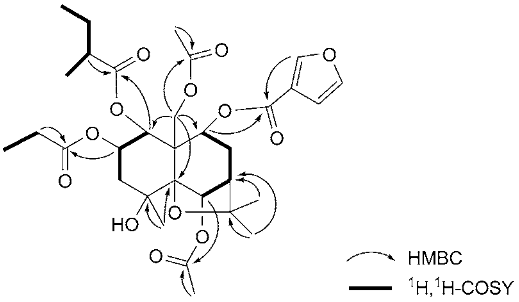

Fig. 4. *Selected 2D-NMR correlations of* **2**

Table 2. *^{1}H- and ^{13}C-NMR Data* (500 and 125 MHz, resp.; CD_3OD) *of* **2**[1]). δ in ppm, *J* in Hz.

Position	δ(H)	δ(C)
H–C(1)	5.54 (*d*, *J* = 3.0)	69.8 (*d*)
H–C(2)	5.45 – 5.47 (*m*)	68.0 (*d*)
CH_2(3)	2.10 (*dd*, *J* = 3.5, 15.5, H_a), 1.91 – 1.97 (*m*, overlapped, H_b)	42.0 (*t*)
C(4)		69.8 (*s*)
C(5)		91.2 (*s*)
H–C(6)	6.07 (*s*)	78.2 (*d*)
H–C(7)	2.12 – 2.14 (*m*)	49.2 (*d*)
CH_2(8)	2.49 (*ddd*, *J* = 3.5, 7.0, 16.0, H_a), 2.21 (*dd*, *J* = 2.0, 16.0, H_b)	34.6 (*t*)
H–C(9)	5.17 (*d*, *J* = 7.0)	69.2 (*d*)
C(10)		55.0 (*s*)
C(11)		84.6 (*s*)
Me(12)	1.43 (*s*)	25.7 (*q*)
Me(13)	1.50 (*s*)	29.5 (*q*)
Me(14)	1.41 (*s*)	25.1 (*q*)
CH_2(15)	4.96 (*d*, *J* = 13.0, H_a), 4.35 (*d*, *J* = 13.0, H_b)	65.7 (*t*)
FuO–C(9)		161.9 (*s*)
	7.97 (*s*)	149.0 (*d*)
	7.37 (*d*, *J* = 1.0)	143.9 (*d*)
		118.8 (*s*)
	6.68 (*d*, *J* = 1.0)	110.0 (*d*)
PrpO–C(2)		173.0 (*s*)
	2.33 (*q*, *J* = 7.5)	28.1 (*t*)
	1.12 (*t*, *J* = 7.5)	9.1 (*q*)
MeBuO–C(1)		174.5 (*s*)
	1.91 – 1.97 (*m*, overlapped)	40.9 (*d*)
	1.24 – 1.32 (*m*)	25.6 (*t*)
	0.98 – 1.07 (*m*)	
	0.84 (*d*, *J* = 7.5)	15.8 (*q*)
	0.63 (*t*, *J* = 7.5)	11.4 (*q*)
AcO–C(6)	2.07 (*s*)	170.4 (*s*), 21.7 (*q*)
AcO–C(15)	2.22 (*s*)	170.7 (*s*), 21.4 (*q*)

173.05 (C=O of PrpO), H–C(6) (δ(H) 6.07)/δ(C) 170.41 (C=O of AcO), H–C(9) (δ(H) 5.17)/δ(C) 161.95 (C=O of FuO), and CH_2(15) (δ(H) 4.35 and 4.96)/δ(C) 170.74 (C=O of AcO). The NOESY experiment revealed the correlations δ(H) 5.54 (H–C(1))/δ(H) 5.46 (H–C(2)) and 6.68 and 7.97 (FuO–C(9)), δ(H) 6.07 (H–C(6))/δ(H) 2.12 – 2.14 (H–C(7)), 1.41 (Me(14)), 1.43 (Me(12)), and 4.35 (H_b–C(15)), and δ(H) 4.35 (H_b–C(15))/δ(H) 5.17 (H–C(9)). Thus the relative positions of these substituent groups were determined. All these data and comparison with those given in [23] established the structure of **2**.

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(10DZ2251300), and the *Scientific Foundation of Shanghai*, P. R. China (09DZ1975700, 09DZ1971500,10DZ1971700, and 11QA1408200).

Experimental Part

General. Column chromatography (CC): silica gel (SiO_2, 200–300 or 300–400 mesh; *Yantai Jiangyou Silica Gel Limited Company*, Yantai, P. R. China), *Sephadex LH-20* (*Pharmacia Fine Chemicals*, Piscataway, NJ, U.S.A.), and *ODS* (*Merck*, Germany). TLC and prep. TLC: *HSGF-254* silica gel plates (SiO_2, 10–40 μm; *Yantai Jiangyou Silica Gel Limited Company*, Yantai, P. R. China). Optical rotations: *Perkin-Elmer-341* digital polarimeter. UV Spectra: *Shimadzu-UV-2550* spectrophotometer; λ_{max} in nm. IR Spectra: *Bruker-Vector-22* spectrophotometer; KBr pellets; $\tilde{\nu}$ in cm^{-1}. NMR Spectra: *Varian-500* (500 MHz) and *Bruker-Avance-400* spectrometers; δ in ppm rel. to Me_4Si as internal standard, J in Hz. MS: *Agilent-1100-LC/MSD-Trap* (ESI) and *Agilent-6520 Q-Tof* (HR-ESI) spectrometers; in *m*/*z*.

Plant Material. The stems of *Euonymus alatus* were collected from Kunming, Yunnan Province, P. R. China, in May 2009 and authenticated by Professor *Li-Shan Xie* of the Kunming Institute of Botany. A voucher specimen (No. 200905003) was deposited with the Herbarium of the School of Pharmacy, Second Military Medical University.

Extraction and Isolation. The dried stems of *Euonymus alatus* (15 kg) were chopped and extracted at r.t. with 95% EtOH (5 ×). The extract was concentrated, then diluted with H_2O and partitioned successively with petroleum ether and AcOEt. The petroleum ether extract (479 g) was subjected to CC (SiO_2, petroleum ether/acetone 50:1 → 1:1): *Fractions 1–16*. *Fr. 5* (3.4 g) was subjected to CC (*ODS*, MeOH/H_2O 1:1 → 4:1; then *Sephadex LH-20*, MeOH) and prep. TLC (MeCl/MeOH 30:1): **2** (28.5 mg), **6** (50.2 mg), and **7** (26.1 mg). *Fr. 7* (7.2 g) was purified by CC (*ODS*, MeOH/H_2O 1:2 → 5:1; then *Sephadex LH-20*, MeOH) and prep. TLC (MeCl/AcOEt/MeOH 8:1:0.1): **1** (11.0 mg), **3** (26.0 mg), **4** (32.2 mg), and **5** (10.9 mg).

rel-*[(1*R*,4*S*,4a*S*,7*S*)-1,2,3,4,4a,5,6,7-Octahydro-4-hydroxy-7-(1-hydroxy-1-methylethyl)-4a-methylnaphthalen-1-yl]methyl 3-Methylbutanoate* (**1**): Colorless oil. $[\alpha]_D^{20} = +38.0$ ($c = 0.25$, MeOH). UV (MeOH): 224. IR (KBr): 3436, 2960, 2871, 1733, 1617, 1467, 1382, 1295, 1191, 1014. ^1H- and ^{13}C-NMR (CD_3OD): *Table 1*. ESI-MS: 361 ($[M + Na]^+$). HR-ESI-MS: 361.2345 ($[M + Na]^+$, $C_{20}H_{34}NaO_4^+$; calc. 361.2355).

rel-*(3*R*,5*S*,5a*R*,6*R*,7*S*,9*S*,9a*S*,10*R*)-10-(Acetyloxy)-5a-[(acetyloxy)methyl]octahydro-9-hydroxy-2,2,9-trimethyl-6-(2-methyl-1-oxobutoxy)-7-(1-oxopropoxy)-2*H*-3,9a-methano-1-benzoxepin-5-yl Furan-3-carboxylate* (**2**): White powder. $[\alpha]_D^{20} = +40.0$ ($c = 0.25$, MeOH). UV (MeOH): 217. IR (KBr): 3445, 2975, 2936, 2879, 1749, 1718, 1462, 1386, 1312, 1245, 1158. ^1H- and ^{13}C-NMR ($CDCl_3$): *Table 2*. ESI-MS: 659 ($[M + Na]^+$). HR-ESI-MS: 659.2706 ($[M + Na]^+$, $C_{32}H_{44}NaO_{13}^+$; calc. 659.2674).

Evonine (**3**): Colorless solid. $C_{36}H_{43}NO_{17}$. ^1H- and ^{13}C-NMR: matching data in [6]. ESI-MS: 784 ($[M + Na]^+$). An X-ray diffraction analysis of **3** (*Fig. 5*) established its absolute configuration.

X-Ray Diffraction Analysis of Evonine (**3**)[2]). A single crystal for analysis was obtained from $CHCl_3$/MeOH/H_2O. Data collection was performed with a *Bruker-APEX2-CCD* instrument and graphite-monochromated CuK_α radiation (λ 1.54178 Å) at 133 (2) K. Crystallgraphic data: $2\,C_{36}H_{43}NO_{17} \cdot 2\,MeOH \cdot 3\,H_2O$; M_r 1641.56; crystal size 0.20 × 0.18 × 0.16 mm; orthorhombic, space group $P2_12_12_1$; $a = 13.0561$ (3) Å, $b = 13.3515$ (3) Å, $c = 46.4680$ (9) Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$; $V = 8100.2$ (3) Å^3; $Z = 4$; $D_x = 1.346$ g cm^{-3}; $F(000) = 3480$; μ(CuK_α) 0.934 mm^{-1}. Cell refinement and data reduction: The *Bruker* SAINT program was used to solve and refine the structure. SHELXS-97 and SHELXL-97, were used for the refinement on F^2 with full-matrix least-squares calculations. All non-H-atoms were filtered with anisotropic parameters, and all H-atoms were positioned by geometrical calculation and refined by the ride-on method with relative isotropic parameters. Absorption correction were applied with semiempirical test from equivalents (max; min. transmission 0.8649;0.8352). In the range $\theta = 1.90°$ to

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[2]) CCDC-838407 contains the supplementary crystallographic data for this article. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request/cif.

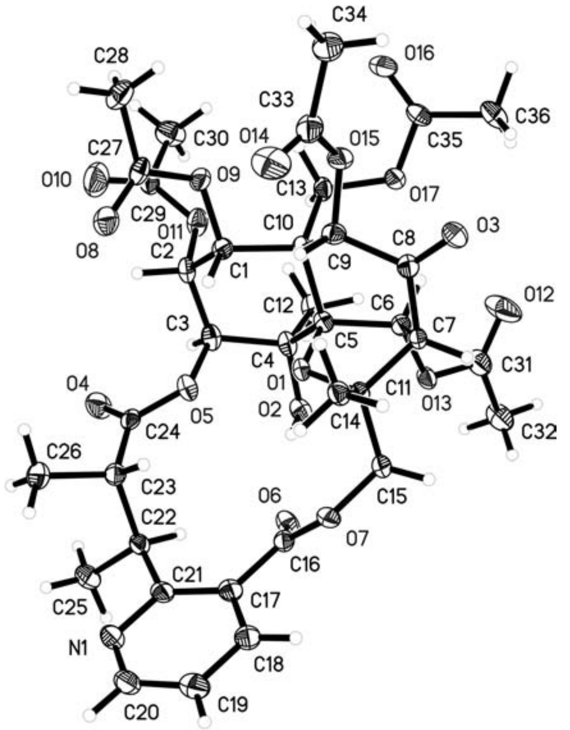

Fig. 5. *X-Ray crystal structure of* **3** (arbitrary atom numbering)

65.00° and limiting indices $14 \geq h \geq -13$, and $15 \geq k \geq -15$, and $54 \geq l \geq -54$, 57689 reflections (13507 unique, $R_{\text{int}} = 0.0327$) were measured. The final phase converged to $R_1 = 0.0580$ ($wR_2 = 0.1617$) for 13507 observed reflections ($I > 2\sigma(I)$) and 1040 refined parameters, $R_1 = 0.0591$ ($wR_2 = 0.1626$) for all unique reflections, and goodness-of-fit on F^2 1.084.

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