New Diels-Alder Reactions of (–)-Thebaine and First X-Ray Crystallographic Structure Analyses of the Cycloadducts

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Diels-Alder reactions of (–)-thebaine (**1**) as an electron-rich diene system with acceptor-substituted ethenes gave rise to the cycloadducts **2**, **3**, and **4** in high regio- and stereoselectivities. Structural analyses were performed by high resolution NMR spectroscopy and, for the first time in the thebaine cycloadduct series, by X-ray crystallographic structural analyses of the compounds **2**, **3a**, and **3b**. In the reaction of (–)-thebaine (**1**) with an *in situ* generated aryne, the anellated azocine derivative **5** was formed.

Diels-Alder reactions of the opium alkaloid (–)-thebaine (**1**) as an electron-rich diene have been the subject of several investigations, in particular in the field of medicinal chemistry for the development of drugs with analgesic activities [1–5]. Recently, we have fulfilled the demand for more precise information on the stereochemistries of some reinvestigated and newly synthesized cycloadducts of thebaine by means of high resolution ¹H-NMR spectroscopy [6]. It was concluded that the β -face *endo* approach [6] of the dienophile to the cyclohexadiene ring C in **1** is unambiguously favoured on steric and electronic grounds; moreover, in the latter case, the experimental results are fully compatible with frontier molecular orbital considerations [6]. In the context of our current investigations on the cycloaddition reactions of various electron-rich heterocycles [7], we are also continuing our studies of these special Diels-Alder reactions with (–)-thebaine (**1**), because the results will be of general interest for the future development of drugs.

In this paper, we describe some further Diels-Alder reactions of (–)-thebaine (**1**) with selected carbodienophiles and report the first X-ray crystallographic structural analyses of Diels-Alder adducts of thebaine. These structural investigations will most certainly shed new light on the some-

times rather unclear and less convincing configurational data given in the earlier reports [1–4] and, last but not least, also provide incontrovertible sustenance for our recent, more detailed report [6].

Results and Discussion

Synthetic aspects

(–)-Thebaine (**1**) reacts with divinylsulfone regio- and stereoselectively to furnish the Diels-Alder product **2** (63% yield). No other isomeric cycloadducts were detected by TLC. However, this product was previously described in ref. [8], but no fully convincing data for the (absolute) stereochemistry of the newly formed stereocentres were given. The structure of **2** has now been unambiguously elucidated by NMR spectroscopy and X-ray crystallography (see below and Fig. 2). According to semiempirical quantum mechanical AM1 calculations [9] (for details see [6]), the dienophile attacks the β side of the diene system and the thus resulting *endo*-transition state is energetically favoured by HOMO(*diene*)-LUMO(*dienophile*) interactions involving secondary orbital overlap [10]. In further experiments, we examined the Diels-Alder reactivity of **1** towards some (*E*)- and (*Z*)-1,2-ethenedicarboxylates and found that **1** reacts with dimethyl and diethyl fumarate to give the cycloadducts **3a** and **3b** stereoselectively (by TLC) in 48 and 52% yields, respectively. In these cases also, the stereochemistries were clarified by NMR spectroscopy and X-ray crystallography (see Fig. 3). In summary, the three

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performed X-ray structural analyses of products **2**, **3a**, and **3b** are unique in the Diels-Alder chemistry of thebaine and further substantiate the structural investigations on the previous Diels-Alder adducts prepared from **1** [6].

It is known that (*Z*)-dialkyl 1,2-ethenedicarboxylates are, in general, less reactive than their (*E*)-counterparts [12]. Thus, in our hands, dimethyl maleate reacted with **1** to give a lower yield (28%) of the cycloadduct **4** [11], albeit stereoselectively. The stereoselective Diels-Alder reactions of (–)-thebaine (**1**) with these dialkyl 1,2-ethenedicarboxylates suggest the exclusive participation of a concerted mechanism.

Acetylenic dienophiles react, in some cases, with (–)-thebaine (**1**) *via* a one-bond addition and subsequent piperidine ring enlargement reaction to

yield polycyclic azocine derivatives [13–15]. We have now found that an *in situ* generated aryne is also able to effect a ring enlargement reaction in **1**. Thus, (–)-thebaine (**1**) reacted with benzyne, readily generated from diazotized anthranilic acid [16], to give rise to the hexacyclic benzo[*b*]naphtho[2,1-*e*]azocine **5**, albeit only in 6% yield together with several other, less stable products. However, no normal Diels-Alder product could be isolated from crude reaction mixture. As a mechanistic rationale for this reaction, we propose a primary nucleophilic attack of the piperidine nitrogen atom at one aryne sp-centre [17]. The thus formed intermediate is then stabilized by heterolytic C9–N σ -bond cleavage which initiates the piperidine ring enlargement reaction (for an analogous mechanistic explanation, see ref. [14]).

NMR spectroscopic investigations

The ^1H and ^{13}C NMR spectroscopic data of the new Diels-Alder adducts are fully compatible with the recently reported data [6]. Typical for the stereochemistry of the Diels-Alder products is, for example, the W-coupling of H 5 with H 17 (approx. 1.20 Hz). Additionally, ^1H , ^1H NOE measurements are frequently useful to obtain more configura-

Fig. 1. ^1H , ^1H -Nuclear Overhauser effects of compound **5** (400 MHz). An INDOR effect is registered between H12 and H13. The given geometry was established by MMX force field calculations and represents a local minimum [19].

Table I. Crystallographic data and structure determination details for **2**, **3a** and **3b**.

Crystal data	2 (KE 27) ¹	3a (KE 14) ¹	3b (KE 16) ¹
Formula, M_r	$C_{23}H_{27}NO_5S$	$C_{25}H_{29}NO_7$	$C_{27}H_{33}NO_7$
Crystal size (mm ³)	$0.21 \times 0.42 \times 0.13$	$0.35 \times 0.06 \times 0.1$	$0.3 \times 1.0 \times 0.6$
Crystal system	monoclinic	orthorhombic	monoclinic
Space group	$P2_1$	$P2_12_12_1$	$P2_1$
Unit cell	$a(\text{\AA})$ $b(\text{\AA})$ $c(\text{\AA})$ $\beta(^{\circ})$	10.639(1) 11.017(1) 18.784(1)	10.9925(2) 8.3447(1) 14.3062(5) 100.790(3)
Determined from	75 refl. $\theta = 65-70^{\circ}$	31 refl. $\theta = 63-70^{\circ}$	75 refl. $\theta = 65-70^{\circ}$
Packing: $V(\text{\AA}^3)$, $F(000)$	1011.72(4), 440.0	2201.8(4), 968.0	1289.10(6), 516.0
$Z, d_{\text{calc}}(\text{g cm}^{-3})$	2, 1.416	4, 1.374	2, 1.246
$\mu(\text{cm}^{-1})$	11.39	8.3	6.53
Data Collection			
Radiation, diffractometer, scan type, temperature		Cu–K α graphite monochromator Enraf-Nonius CAD 4, $\Omega/2\theta$, 298 K	
θ Range	$1.5^{\circ} \leq \theta \leq 70.0^{\circ}$	$2.0^{\circ} \leq \theta \leq 70.0^{\circ}$	$2.0^{\circ} \leq \theta \leq 70.0^{\circ}$
Range of hkl	$0 \leq h \leq 11$ $-8 \leq k \leq 0$ $-18 \leq l \leq 18$	$0 \leq h \leq 12$ $0 \leq k \leq 13$ $0 \leq l \leq 22$	$0 \leq h \leq 14$ $-11 \leq k \leq 0$ $-18 \leq l \leq 18$
Reflections: meas., Indep., R_{int}	4386 3796, 0.02	4710 4107, 0.03	5414 4754, 0.02
Friedel-pairs used, limit ($F/\sigma(F) >$)	measured 3768, 4	measured 3614, 4	measured 4707, 4
Refinement			
	Hydrogen atoms located from difference Fourier calculations		
Choice of displ. parameters:			
non-Hydrogen	anisotropic	anisotropic	anisotropic
Hydrogen	riding, isotropic	riding, isotropic	riding, isotropic
Variables	286	327	334
Last shift (*esd)	0.001	0.001	0.01
Final R , R_w	0.038 (0.054		0.050, 0.062
wR_2 , $R1$	other enantiomer)	0.114, 0.042	
Flack-Parameter	–	–0.2(2)	–
Weighting scheme	unit	$1/[(\sigma^2(F_o^2) + (0.0611 * P)^2 + 0.26 * P)]$	$1/(\sigma^2(F_o^2) + 0.0045 * F_o^2)$
P	–	(Max(F_o^2 , 0) + 2 * F_c^2)/3	–
Goodness of fit	–	1.044	1.24
Extinction parameter	–	0.0007(2)	0.035(2)
Final difference Fourier maxima ($e\text{\AA}^{-3}$)	0.42, –0.57	0.18, –0.14	0.51, –0.49
Used programs:			
Solution	SHELXS-86 [20]	SHELXS-86	SHELXS-86
Method	Direct Methods	Direct Methods	Direct Methods
Refinement	SHELXL-93 [21]	SHELX-76 [22]	SHELX-76
Scattering factors from geometrical calculations	SHELXL-93 GEOM [24]	SHELX-76 GEOM	SHELX-76 GEOM

¹ Substance code in supplemental material.

tional details about the newly formed stereocentres. In the case of compound **3a**, interatomic distances were exemplarily analyzed by NOE experiments (steady state NOE) and proton T_1 measurements [18]. On the basis of a calculated (fixed) H–H reference distance (averaged distance H5–H,H15a,b by MMX molecular mechanics method = 2.58 Å [19]), the configurations at C7 and C8 were established. In summary, the relevance of more sophisticated NMR spectroscopic configuration analysis in the thebaine cycloadduct series is nicely illustrated by these studies in combination with the X-ray crystallographic results.

In the case of the hexacyclic product **5**, firstly the diagnostically relevant $^1\text{H},^1\text{H}$ NOE's from H17 to N5–CH₃ and vice versa (averaged H–H distance of approx. 3.2 Å according to MMX force field calculations [19], see also Fig. 1), in addition, a paramagnetic shift of the signal for H17 of approx. 0.5 ppm in comparison to the analogous shift in the thebaine cycloadducts and an H,H–COSY spectrum are highly indicative for the structure of **5** given.

X-ray crystallographic structural analyses of 2, 3a, and 3b

Experimental details for the structural analyses of compounds **2**, **3a**, and **3b** are listed in Table I. The investigated compounds all crystallized in non-centrosymmetric space groups, thus only one enantiomer is present in each case. As shown in Table II, the most important geometrical parameters for the compounds are all equal within the limits of accuracy and lie in the normal range. The phenyl ring is approximately planar, the five-membered ring C4, C12, C13, C5, O1 is twisted with C5 being above and C13 being below the least squares plane. As shown in Fig. 2, it can be concluded from the least squares calculations and from the values of the torsional angles that the cyclohexane ring has the boat conformation, while the piperidine ring takes up the chair conformation. The etheno bridge C6–C17–C18–C14 is nearly perpendicular to the least squares plane of the cyclohexane ring.

Further details of X-ray structural analyses can be obtained on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eg-

genstein-Leopoldshafen, Germany, on quotation of the deposition number CSD-57719, the authors names, and the full journal citation.

Table II. Selected bond lengths for **2**, **3a** and **3b**.

Bond	2	3a	3b
O1–C4	1.394(4)	1.377(3)	1.376(2)
O1–C5	1.452(4)	1.471(3)	1.465(2)
N1–C9	1.487(4)	1.473(3)	1.471(3)
N1–C16	1.468(5)	1.456(4)	1.465(3)
C1–C2	1.394(5)	1.401(4)	1.404(4)
C1–C11	1.392(5)	1.394(3)	1.394(4)
C2–C3	1.399(6)	1.390(3)	1.396(4)
C3–C4	1.377(5)	1.389(3)	1.387(3)
C4–C12	1.383(5)	1.373(3)	1.385(2)
C5–C6	1.563(4)	1.543(3)	1.539(2)
C5–C13	1.542(4)	1.536(3)	1.545(2)
C6–C7	1.577(5)	1.573(3)	1.582(2)
C6–C17	1.495(5)	1.514(3)	1.508(3)
C7–C8	1.569(4)	1.548(3)	1.560(2)
C8–C14	1.541(5)	1.571(3)	1.542(3)
C9–C10	1.556(5)	1.572(3)	1.567(3)
C9–C14	1.544(4)	1.542(3)	1.552(3)
C10–C11	1.514(5)	1.515(4)	1.528(3)
C11–C12	1.383(5)	1.372(3)	1.373(3)
C12–C13	1.495(5)	1.499(3)	1.498(3)
C13–C14	1.541(5)	1.565(3)	1.563(2)
C13–C15	1.545(5)	1.537(3)	1.539(3)
C14–C18	1.520(5)	1.510(3)	1.515(3)
C15–C16	1.525(5)	1.521(4)	1.516(3)
C17–C18	1.317(4)	1.321(3)	1.332(3)

Fig. 2. X-ray structure of **2**, SCHAKAL plot [23].

Fig. 3. X-ray structures of **3a** (above) and **3b** (below), SCHAKAL plot [23]. A disorder was found at C27. One of the possible orders was chosen.

Experimental

¹H NMR spectra were recorded at 200 and 400 MHz with Bruker AC 200 and AMX 400 spectrometers. ¹³C NMR spectra were measured at 50.3 MHz with a Bruker AC 200 instrument; *J*-modulated spin echo spectra were obtained in all cases (*C*_p = primary, *C*_s = secondary, *C*_t = tertiary, and *C*_q = quaternary carbon atoms). The EI (70 eV) mass spectra were recorded on a Varian MAT 7 spectrometer. Elemental analyses were performed by using a Carlo Erba Strumentazione 1106 apparatus. Melting points were measured with an Electrothermal 8200 instrument. Flash chromatography was performed on Merck 60 silica gel (particle size: 0.040–0.063 mm). The petroleum ether used had the boiling range 40–60 °C.

All reactions were performed in highly pure, anhydrous solvents. The yields given refer to analytically pure compounds, some product loss occurred during chromatographic work-up.

4,5*a*-Epoxy-3,6-dimethoxy-*N*-methyl-7*a*-vinylsulfonfyl-6*a*, 14*a*-endo-etheno-isomorphinan (2)

(–)-Thebaine (**1**) (200 mg, 0.64 mmol) was dissolved in 20 ml toluene. After addition of divinylsulfone (75.6 mg, 0.64 mmol), the mixture was stirred for 24 h at 20 °C. The formed precipitate was recrystallized four times from ethyl acetate/petroleum ether. Yield 170 mg (63%), m.p. 188–190 °C (ethyl acetate, petroleum ether), 190–192 °C [8]. – ¹H NMR (200 MHz, CDCl₃): δ = 1.81 (m_c, 4H), 2.33 (s, 3H, NCH₃), 2.43 (m_c, 3H), 3.2 (m_c, 3H), 3.68 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 4.45 [d, 1H, *J*(H5, H17) 1.19 Hz, W-coupling, H5], 5.51 [d, 1H, *J*(H18, H17) 8.88 Hz, H18], 6.00 (m_c, 2H, H17 and –CH=CH₂), 6.30 [d, 1H, *J*(E–CH=CH₂–CH=CH₂) 16.82 Hz, –CH=CH₂], 6.52 [d, 1H, *J*(H1, H2) 8.20 Hz, H1], 6.62 (d, 1H, *J*(H2, H1) 8.07 Hz, H2], 6.79 [dd, 1H, *J*(E–CH=CH₂–CH=CH₂) 16.65 Hz, *J*(Z–CH=CH₂–CH=CH₂) 9.81 Hz, –CH=CH₂]. – ¹³C NMR (50.3 MHz, CDCl₃): δ(*C*_p) = 43.40, 54.15, 56.62 (1×NCH₃, 2×OCH₃); δ(*C*_s) = 22.35, 28.25, 33.24, 42.75, 45.25 (C8, C10, C15, C16, –CH=CH₂); δ(*C*_t) = 59.70, 62.93, 95.47 (C5, C7, C9), 113.71, 119.77, 125.11 (C17, C18, –CH=CH₂), 135.48, 138.93 (C1, C2); δ(*C*_q) = 47.08, 80.16, 128.04 (C6, C13, C14), 128.06, 133.65, 142.50, 147.61 (C3, C4, C11, C12). – EI-MS: *m/z* (%) = 429 (16) [M]⁺, 338 (43).

C₂₃H₂₇NSO₅ (429.54)

Calcd	C 64.31	H 6.34	N 3.26	S 7.46%
Found	C 64.52	H 6.45	N 3.16	S 7.60%

4,5*a*-Epoxy-7β,8*a*-bis(methoxycarbonyl)-3,6-dimethoxy-*N*-methyl-6*a*, 14*a*-endo-etheno-isomorphinan (3a)

(–)-Thebaine (**1**) (200 mg, 0.64 mmol) and dimethyl fumarate (365 mg, 3.2 mmol) were heated under reflux in 30 ml toluene for 4 d. The mixture was then concentrated to 1 ml and the residue obtained was purified by flash chromatography (ethyl acetate/petroleum ether 3:1). Yield 140 mg (48%), m.p. 159–162 °C (ethyl acetate). – ¹H NMR (200 MHz, CDCl₃): δ = 1.72 [dd, 1H, *J*(H15, H15) 13.53 Hz, *J*(H15, H16) 2.87 Hz, H15], 2.34 (s, 3H, NCH₃), 2.50 (m_c, 3H, H10, 2×H16), 2.82 (m_c, 1H, H15), 3.05 [d, 1H, *J*(H7, H8) 5.61 Hz, H7], 3.22 (d, 1H, *J*(H10, H10) 18.58 Hz, H10), 3.54 (s, 3H, OCH₃), 3.57 [d, 1H, *J*(H9, H10) 6.79 Hz, H9], 3.68 (s, 3H, COOCH₃), 3.77 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 4.16 [d, 1H, *J*(H8, H7) 5.57 Hz, H8], 4.93 [d, 1H, *J*(H5, H17) 1.04 Hz, W-coupling, H5], 5.49 [d, 1H, *J*(H18, H17) 8.88 Hz, H18], 6.06 [dd, 1H, *J*(H17, H18) 8.94 Hz, *J*(H17, H5) 1.20 Hz, W-coupling, H17], 6.51 [d, 1H, *J*(H2, H1) 8.14 Hz, H2], 6.62 [d, 1H, *J*(H1, H2) 8.14 Hz, H1]. – ¹³C NMR (50.3 MHz, CDCl₃): δ(*C*_p) = 43.81, 44.62, 50.01, 52.28, 52.70 (1×NCH₃, 4×OCH₃); δ(*C*_s) = 22.95, 30.88, 45.55 (C10, C15, C16); δ(*C*_t) = 52.87, 57.17, 58.50, 92.37 (C5, C7, C8, C9), 114.43, 119.85 (C17, C18), 127.25, 136.05 (C1, C2); δ(*C*_q) = 46.04, 48.10, 81.65 (C6, C13, C14), 128.27, 135.06, 142.58, 148.18 (C3, C4, C11, C12), 173.14, 173.74 (2×CO). – EI-MS: *m/z* (%) = 455 (69) [M]⁺, 311 (13).

C₂₅H₂₉NO₇ (455.52)

Calcd	C 65.92	H 6.42	N 3.07%
Found	C 65.96	H 6.37	N 3.16%

4,5*a*-Epoxy-7β,8*a*-bis(ethoxycarbonyl)-3,6-dimethoxy-*N*-methyl-6*a*, 14*a*-endo-etheno-isomorphinan (3b)

From (–)-thebaine (**1**) (200 mg, 0.64 mmol) and diethyl fumarate (551 mg, 3.2 mmol) following the procedure described above for compound **3a**. Yield 160 mg (52%), m.p. 108–110 °C (ethyl acetate). – ¹H NMR (200 MHz, CDCl₃): δ = 1.27 (m_c, 6H, 2×OCH₂CH₃), 1.70 [dd, 1H, *J*(H15, H15) 13.65 Hz, *J*(H15, H16) 2.71 Hz, H15], 2.34 (s, 3H, NCH₃), 2.50 (m_c, 3H, H10, 2×H16), 2.84 (m_c, 1H, H15), 3.02 [d, 1H, *J*(H7, H8) 5.71 Hz, H7], 3.21 [d, 1H, *J*(H10, H10) 18.58 Hz, H10], 3.54 (s, 3H, OCH₃), 3.61 [d, 1H, *J*(H9, H10) 6.52 Hz, H9], 3.80 (s, 3H, OCH₃), 4.20 (m_c, 5H, H8, 2×OCH₂CH₃), 4.94 [d, 1H, *J*(H5, H17) 1.40 Hz,

W-coupling, H 5], 5.49 [d, 1 H, J (H 18; H 17) 8.85 Hz, H 18], 6.05 [dd, 1 H, J (H 17, H 18) 8.87 Hz, J (H 17, H 5) 1.43 Hz, H 17], 6.51 [d, 1 H, J (H 1, H 2) 8.19 Hz, H 1], 6.62 [d, 1 H, J (H 2, H 1) 8.11 Hz, H 2]. – ^{13}C NMR (50.3 MHz, CDCl_3): $\delta(\text{C}_\text{p})$ = 14.20, 14.24, 43.44, 44.16, 50.14 (NCH_3 , $2 \times \text{OCH}_3$, $2 \times \text{OCH}_2\text{CH}_3$); $\delta(\text{C}_\text{s})$ = 22.46, 30.19, 45.11, 60.70, 61.21 (C 10, C 15, C 16, $2 \times \text{OCH}_2\text{CH}_3$); $\delta(\text{C}_\text{t})$ = 52.71, 56.86, 57.97, 91.99 (C 5, C 7, C 8, C 9), 114.15, 119.24 (C 17, C 18), 127.07, 135.35 (C 1, C 2); $\delta(\text{C}_\text{q})$ = 45.47, 47.60, 81.13 (C 6, C 13, C 14), 127.54, 134.56, 142.11, 147.73 (C 3, C 4, C 11, C 12), 172.31, 173.05 ($2 \times \text{CO}$). – EI-MS: m/z (%) = 483 (100) $[\text{M}]^+$, 311 (21).

Analysis $\text{C}_{27}\text{H}_{33}\text{NO}_7$ (483.57)

Calcd C 67.06 H 6.88 N 2.90%,
Found C 67.12 H 6.75 N 3.02%.

4,5- α -Epoxy-7 α ,8 α -bis(methoxycarbonyl)-3,6-dimethoxy-N-methyl-6 α ,14 α -endo-etheno-isomorphinan (4)

(–)-Thebaine (**1**) (200 mg, 0.64 mmol) and dimethyl maleate (553.5 mg, 3.84 mmol) were heated under reflux in 30 ml toluene for 4 d. The mixture was then concentrated to 1 ml and stored for 24 h at 6 °C. The formed solid product was crystallized several times from methanol. Yield 80 mg (28%), m.p. 188–190 °C, 189–190 °C [11 a]. – ^1H NMR (200 MHz, CD_2Cl_2): δ = 1.83 (m_c , 1 H, H 15), 1.95 (m_c , 1 H, H 15), 2.30 (s, 3 H, NCH_3), 2.38 (m_c , 1 H, H 16), 2.49 (m_c , 2 H, H 10, H 16), 3.19 [d, 1 H, J (H 10, H 10) 18.66 Hz, H 10], 3.36 [d, 1 H, J (H 7, H 8) 11.12 Hz, H 17], 3.50 (s, 3 H, OCH_3), 3.53 (s, 3 H, OCH_3), 3.61 (s, 3 H, OCH_3), 3.74 [d, 1 H, J (H 9, H 10) 6.62 Hz, H 9], 3.78 (s, 3 H, OCH_3), 4.14 (d, 1 H, J (H 8, H 7) 11.14 Hz, H 8], 4.59 [d, 1 H, J (H 5, H 17) 0.91 Hz, W-coupling, H 5], 5.77 [d, 1 H, J (H 18, H 17) 8.85 Hz, H 18], 5.88 [d, 1 H, J (H 17, H 18) 8.83 Hz, H 17], 6.57 [d, 1 H, J (H 1, H 2) 8.17 Hz, H 1], 6.63 [d, 1 H, J (H 2, H 1) 8.18 Hz, H 2]. – ^{13}C NMR (50.3 MHz, CD_2Cl_2): $\delta(\text{C}_\text{p})$ = 43.75, 46.20, 49.11, 51.63, 52.10 ($1 \times \text{NCH}_3$, $4 \times \text{OCH}_3$); $\delta(\text{C}_\text{s})$ = 22.60, 34.04, 45.59 (C 10, C 15, C 16); $\delta(\text{C}_\text{t})$ = 52.68, 56.93, 58.24, 92.97 (C 5, C 7, C 8, C 9), 114.16, 120.05 (C 17, C 18), 126.41, 135.08 (C 1, C 2); $\delta(\text{C}_\text{q})$ = 44.66, 47.77, 81.04 (C 6, C 13, C 14), 128.73, 133.72, 142.30, 148.30 (C 3, C 4, C 11, C 12), 171.43, 171.56 ($2 \times \text{CO}$). – EI-MS: m/z (%) = 455 (100) $[\text{M}]^+$, 311 (23).

Analysis $\text{C}_{25}\text{H}_{29}\text{NO}_7$ (455.52)

Calcd C 65.92 H 6.42 N 3.07%,
Found C 65.81 H 6.38 N 3.21%.

*8,17 α -Epoxy-9,16-dimethoxy-5-methyl-5,6,7,7 α ,12,14 β -hexahydro-7 $\alpha\alpha$,14 α -[1]-propenobenzo[*b*]naphtho[2,1-*e*]azocine (5)*

Anthranilic acid (950 mg, 6.92 mmol) and tri-chloroacetic acid (8.4 mg, 0.05 mmol) were suspended in 20 ml tetrahydrofuran and cooled to 0 °C. To this mixture in over a period of 2 min was added isoamyl nitrite (1.6 ml, 11.8 mmol) at same temperature. After the mixture had been stirred at 20 °C for 1.5 h the precipitate was separated and purified by washing with tetrahydrofuran. The thus obtained *o*-benzene-diazonium carboxylate was suspended in dichloromethane. The resultant suspension was added in small portions to a refluxing solution of (–)-thebaine (**1**) (388.75 mg, 1.25 mmol) in 25 ml dichloromethane over a period of 30 min. After being heated under reflux for 30 min, the mixture was concentrated carefully under reduced pressure and the residue obtained purified by flash chromatography (ethyl acetate/petroleum ether, 3:1). Yield 30 mg (6%), m.p. 186 °C (ethyl acetate). – ^1H NMR (400 MHz, CD_2Cl_2): δ = 1.59 [dd, 1 H, J (H 7, H 7) 13.94 Hz, J (H 7, H 6) 4.38 Hz, H 7], 2.33 (m_c , 1 H, H 6), 2.75 (s, 3 H, NCH_3), 2.94 (m_c , 2 H, H 6, H 7), 3.22 (m_c , 2 H, $2 \times \text{H}$ 12), 3.45 (s, 3 H, OCH_3), 3.84 (s, 3 H, OCH_3), 4.21 [d, 1 H, J (H 14, H 15) 6.07 Hz, H 14], 4.74 [d, 1 H, J (H 15, H 14) 6.14 Hz, H 15], 5.43 (s, 1 H, H 17), 6.14 [dd, 1 H, J (H 13, H 12) = 5.73, J (H 13, H 14) 2.59 Hz, H 13], 6.66 [d, 1 H, J (H 11, H 10) 8.02 Hz, H 10], 6.69 [d, 1 H, J (H 10, H 11) 8.10 Hz, H 10], 6.98 (m_c , 1 H, aromatic), 7.19 (m_c , 3 H, aromatic). – ^{13}C NMR (50.3 MHz, CD_2Cl_2): $\delta(\text{C}_\text{p})$ = 39.24, 49.87, 54.87 ($1 \times \text{NCH}_3$, $2 \times \text{OCH}_3$); $\delta(\text{C}_\text{s})$ = 29.78, 37.23, 60.71 (C 6, C 7, C 12); $\delta(\text{C}_\text{t})$ = 56.87, 88.75 (C 14, C 17), 100.64, 112.41 (C 13, C 15), 119.15, 119.88, 123.65, 125.91, 127.79, 131.43 (C 1, C 2, C 3, C 4, C 10, C 11); $\delta(\text{C}_\text{q})$ = 51.33 (C 7a), 128.79, 136.13 (C 13a, C 16), 139.89, 143.03, 143.31, 145.03, 152.70, 154.76 (C 4a, C 7b, C 8, C 9, C 11a, C 14a). – EI-MS: m/z (%) = 387 (100) $[\text{M}]^+$.

Analysis $\text{C}_{25}\text{H}_{25}\text{NO}_3$ (387.49)

Calcd C 77.49 H 6.50 N 3.61%,
Found C 76.69 H 6.98 N 3.84%.

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