Functionalization of the 6,14-Bridge of the Orvinols
1. Preparation and *Diels–Alder* Reaction of 7-Phenylsilylthebaines

by **Weibin Chen**[a]), **Damon A. Parrish**[b]), **Jeffrey R. Deschamps**[b]), and **Andrew Coop***[a])

[a]) Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, 20 Penn Street, Room 637, Baltimore, MD 21201, USA (phone: (+1)-410-706-2029; e-mail: acoop@rx.umaryland.edu)
[b]) Laboratory for the Structure of Matter, Naval Research Laboratory, Washington, DC 20375, USA

The anion **5** of thebaine (**1**) reacts with small electrophiles exclusively at the 5-position (*Scheme 1*). Reaction of thebaine anion with a range of alkylarylsilyl chlorides showed that reaction at the 7-position was favored with increasing steric bulk, with triphenylsilyl chloride yielding only the 7-substituted product **7e** (*Scheme 1*). Reaction of 7-(triphenylsilyl)thebaine (**7e**) with benzoquinone gave rise to the expected *Diels–Alder* adduct **8** (*Scheme 2*), an analog of thevinone (**2**) with a silyl substituent at the 6,14-etheno bridge. The presence of this substituent gives a handle for potentially functionalizing the bridge of this important class of compounds.

Introduction. – The orvinols are an extremely potent class of opioids deriving from the opium alkaloid thebaine (**1**) (*Fig. 1*) [1–3]. *Diels–Alder* reaction of **1** with various dienophiles yields the thevinones, typified by thevinone (**2**) [4][5]. Further reactions (*Grignard* addition, 3-*O*-demethylation) yield the orvinols such as etorphine (**3**). Most variants of orvinols resulted from altering the substituent at N(17) and the substituent in position 7α of the opioid skeleton [4]. All orvinols possess a 6α,14α-etheno or -ethano bridge, with only rare examples of substitution at the bridge due to severe steric hindrance causing synthetic difficulties. We considered that one potential approach to functionalize the bridge was to introduce a group at the 7-position of thebaine, followed by *Diels–Alder* reaction with dienophiles. To the best of our knowledge, no simple direct routes to 7-substituted thebaines have been reported; only the 7-phenyl derivative **4a** and the 7-chloro-6-demethoxy analog **4b** (*Fig. 1*) were prepared *via* involved syntheses [6][7], and neither are amenable for further functionalization. We describe herein a remarkably simple synthesis of 7-silylthebaines which takes advantage of a regioselective silylation of the anion **5** of thebaine and, after *Diels–*

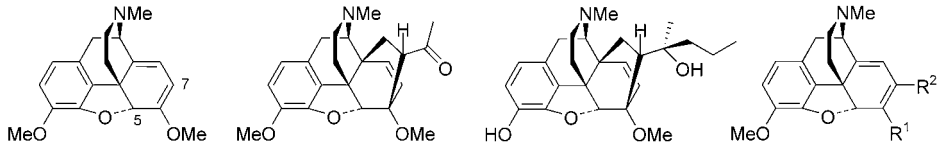
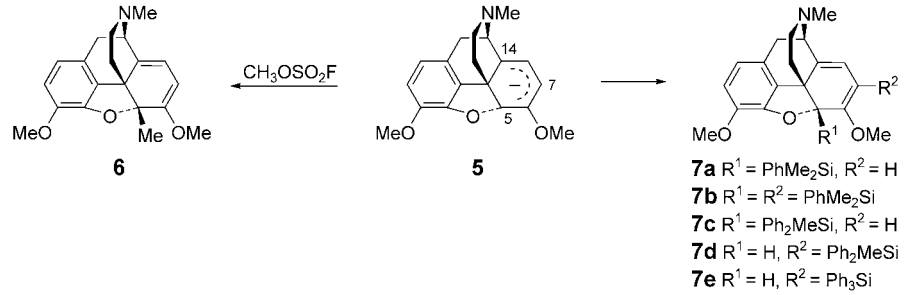


Fig. 1. *Structures of thebaine* (**1**), *thevinone* (**2**), *etorphine* (**3**), *and analogs* (**4**) *of thebaine*

Alder reaction, yields a 18-silylated product which has the potential for further functionalization.

Gates and co-workers first reported deuteration, alkylation, and acylation of thebaine anion (**5**) [8][9], yielding only 5-substituted derivatives such as **6** (*Scheme 1*), and our recent trimethylsilylation and butylation of thebaine anion also occurred at the 5-position exclusively in 97 and 55% yield, respectively [10][11]. According to charge distributions, the 5-, 7-, and 14-positions are three possible nucleophilic substitution centers [12]. The preference for the 5-position presumably reflects the fact that reactions at C(7) or C(14) would place unsaturation between C(5) and C(6), a position at which planarity would result in a strained ring. From the structural point of view, the 5- and 14-positions are more sterically congested than the 7-position. We therefore considered that reaction with bulky electrophiles may favor reaction at the 7-position, and studied a range of silyl agents as they allow for further synthetic manipulation.

Scheme 1



Results and Discussion. – Thebaine anion (**5**) was generated by treatment of **1** with 2 equiv. of BuLi and 2 equiv. of the cation-complexing agent *N*,*N*,*N*′,*N*′-tetramethylethane-1,2-diamine (TMEDA), followed by silylation of the resulting anion with 10 equiv of the silyl chloride. The excess silyl chloride was removed by flash chromatography, and the residue was analyzed by ^{1}H-NMR to determine the crude product ratio. Isolation and further purification by chromatography gave the pure compounds. Product ratios and yields, are summarized in *Table 1*. When the electrophile was the small Me_3SiCl, the reaction was regiospecific for the 5-position in 97% yield [11]. Substituting one Me group with one Ph group caused the formation of two products, one being the 5-substituted thebaine **7a** (35% yield) and the other the 5,7-disubstituted thebaine **7b** (47% yield), the disilylated product obviously arising from a

Table 1. *Silylation of* **1** *with Various Silyl Chlorides*

Silylating agent	Product ratio[a])	Isolated yields[b])
$PhMe_2SiCl$	**7a**/**7b** 8 : 10	**7a** (35%), **7b** (47%)
$Ph_2MeSiCl$	**7c**/**7d** 2 : 7	**7c** (14%), **7d** (62%)
Ph_3SiCl	–	**7e** (64%)

[a]) Product ratio determined by ^{1}H-NMR of crude product mixture. [b]) Yield after isolation and purification.

second deprotonation after initial silylation. Increasing the size of the electrophile to that of diphenylsilyl chloride gave the 5-substituted thebaine **7c** in 14% yield together with the 7-substituted thebaine **7d** in 62% yield. We envision in this case that once one silyl group has been added, the system is too bulky to allow a second to react. Reaction with the triphenylsilyl electrophile gave only the 7-substituted thebaine **7e** in 64% yield, indicating that the substitution reaction occurred regiospecifically at the 7-position.

The structure of the 5-substituted analogs was confirmed through the loss of the H(5) signal in the ^{1}H-NMR, while the olefinic H–C(7) and H–C(8) appear as an *AB* spin system. The structure of **7a** was further confirmed by single-crystal X-ray analysis (*Fig. 2*). The 7-substitution was assumed through the loss of one olefinic proton and the other remaining as a *s*, and was confirmed for **7d** (Ph_2MeSi–C(7)) by NMR (^{1}H, ^{13}C, DEPT, COSY, HSQC, and HMBC) as detailed in *Table 2*.

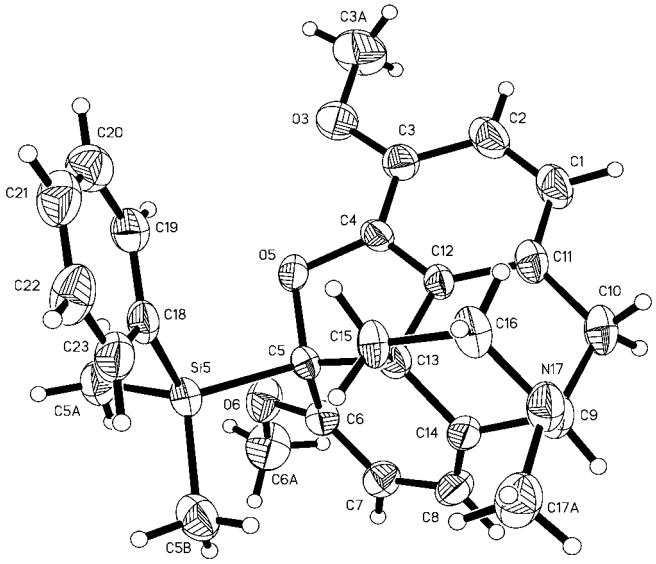


Fig. 2. *X-Ray crystal structure of* **7a**

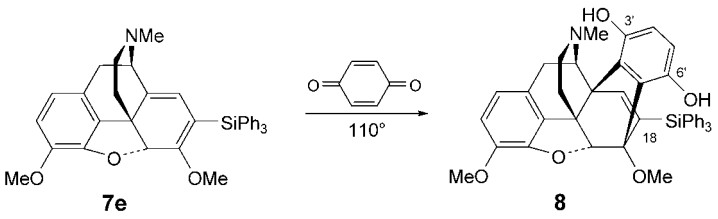
With the 7-substituted thebaines in hand, our investigations focused on exploring the *Diels–Alder* reactions with a dienophile. Reaction of **7e** with 10 equiv. of 1,4-benzoquinone in refluxing toluene gave rise to a single product **8** in 95% yield (*Scheme 2*). The structure of **8** was confirmed to be the quinol form of the expected adduct of the *Diels–Alder* reaction through NMR and single-crystal X-ray analysis (*Fig. 3*). Adduct **8** represents the first true analog of thevinone (**2**) with a substituent suitable for further manipulation on the 6,14-etheno bridge.

Table 2. *^{1}H-NMR* (500 MHz), *^{13}C-NMR* (125 MHz), *^{1}H,^{1}H-COSY, HSQC, and HMBC Data of* **7d**. δ in ppm, J in Hz.

	δ(C)	δ(H)	^{1}H,^{1}H-COSY	HSQC[a]) from H to C	HMBC[a]) from H to C
H–C(1)	119.34	6.59 (*d*, J = 7.8)	6.66	119.34	28.52, 133.10, 142.63, 144.32
H–C(2)	113.28	6.66 (*d*, J = 7.8)	6.59	113.28	127.57, 142.63, 144.32
C(3)	142.63				
*Me*O–C(3)	56.61	3.85 (*s*)		56.61	142.63
C(4)	144.32				
H–C(5)	86.49	5.52 (*s*)		86.49	37.50, 46.40, 131.01, 133.10, 136.70, 144.32, 158.13
C(6)	158.13				
*Me*O–C(6)	55.43	3.49 (*s*)		55.43	158.13
C(7)	136.70				
Ph_2*Me*Si–C(7)	– 3.11	0.66 (*s*)		– 3.11	110.68, 136.70
H–C(8)	115.80	5.38 (*s*)		115.80	46.40, 158.13
H–C(9)	60.87	3.53 (*d*, J = 6.8)	2.59	60.87	
CH_2(10)	28.52	2.59 (*dd*, J = 18.1, 6.8, 1 H)	3.53, 3.30	28.52	
		3.30 (*d*, J = 18.1, 1 H)	2.59	28.52	
C(11)	127.57				
C(12)	133.10				
C(13)	46.40				
C(14)	131.01				
CH_2(15)	37.50	1.77 (*dd*, J = 12.4, 2.0, 1 H)	2.80, 2.23	37.50	
		2.23 (*dt*, J = 12.7, 4.9, 1 H)	1.77, 2.64	37.50	
CH_2(16)	45.90	2.64 (*dd*, J = 12.7, 4.4, 1 H)	2.80, 2.23	45.90	
		2.80 (*dt*, J = 12.4, 3.4, 1 H)	1.77, 2.64	45.90	
Me–N(17)	42.09	2.43 (*s*)		42.09	45.90, 60.87

[a]) δ(C) 86.49 is typical of C(5), and δ(C) – 3.11 is characteristic of Me in $MePh_2Si$. A one-bond HSQC correlation δ(H) 5.52/δ(C) 86.49 allows assignment of *H*–C(5). The position of the $MePh_2Si$ group is established based on two three-bond HMBC correlations δ(H) 5.52/δ(C) 136.70 and δ(H) 0.66/δ(C) 136.70.

Scheme 2



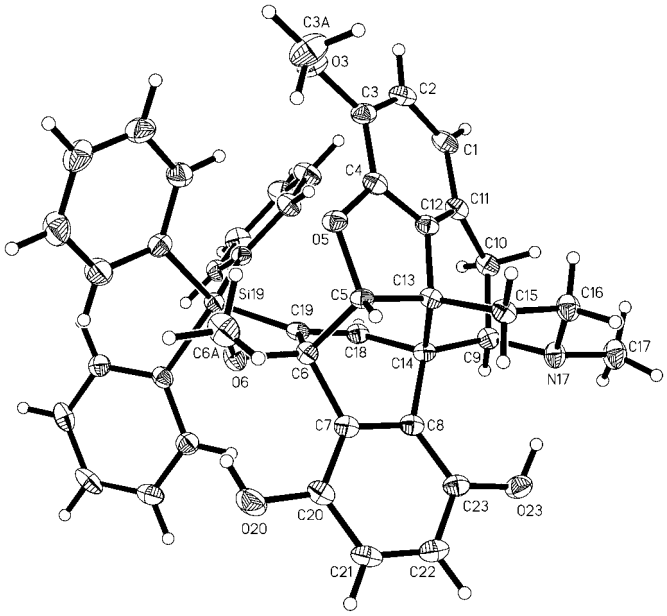


Fig. 3. *X-Ray crystal structure of* **8**

Experimental Part

General. All reactions were preformed under N_2 in dried glassware. Thebaine (**1**) was obtained from *Mallinckrodt Inc.*, and all other reagents were used as obtained from *Sigma–Aldrich*. Solvents were used without purification from *VWR*. Flash column chromatography (FC): silica gel (230–400 mesh).

General Procedure for Silylations: 5-(Dimethylphenylsilyl)thebaine (*=(5β)-6,7,8,14-Tetradehydro-5-(dimethylphenylsilyl)-4,5-epoxy-3,6-dimethoxy-17-methylmorphinan*; **7a**) *and 5,7-Bis(dimethylphenylsilyl)thebaine* (*=(5β)-6,7,8,14-Tetradehydro-5,7-bis(dimethylphenylsilyl)-4,5-epoxy-3,6-dimethoxy-17-methylmorphinan*; **7b**). To a stirred soln. of TMEDA (0.91 ml, 6.0 mmol) in dry THF (10 ml), cooled to $-78°$, was added 1.25M BuLi (in hexane 4.8 ml, 6.0 mmol). The mixture was stirred for 30 min before the slow addition of a soln. of **1** (0.93 g, 3.0 mmol) in dry THF (20 ml). The soln. was stirred at $-78°$ for 1 h. Then a soln. of $PhMe_2SiCl$ (5.1 ml, 30 mmol) in THF (20 ml) was added dropwise. After stirring for a further 30 min at -78^0, the soln. was allowed to come to r.t. over 2 h, and stirred at r.t. for 10 h. The mixture was evaporated, the residue taken into $CHCl_3$ (50 ml), the soln. washed with $NaHCO_3$ soln., H_2O, and brine, dried (Na_2SO_4), and evaporated, and the excess $PhMe_2SiCl$ removed by FC (1% MeOH/CH_2Cl_2). The products in the column were eluted with 20% MeOH/CH_2Cl_2. The product ratio was then determined by NMR. Subsequent FC ($\rightarrow$10% MeOH/CH_2Cl_2) afforded **7a** (0.47 g, 35%) and **7b** (0.82 g, 47%), both as colorless foams.

Data of **7a**: ^{1}H-NMR (500 MHz, $CDCl_3$): 0.55 (*s*, 3 H); 0.57 (*s*, 3 H); 1.39 (*dd*, *J* = 13.2, 2.0, 1 H); 2.21 (*dt*, *J* = 12.9, 5.4, 1 H); 2.48 (*s*, 3 H); 2.61 (*dd*, *J* = 13.2, 3.9 1 H); 2.84–2.93 (*m*, 2 H); 3.48 (*s*, 3 H); 3.50 (*d*, *J* = 18.1, 1 H); 3.87 (*d*, *J* = 6.8, 1 H); 3.92 (*s*, 3 H); 5.01 (*d*, *J* = 6.8, 1 H); 5.71 (*d*, *J* = 6.8, 1 H); 6.58 (*d*, *J* = 7.8, 1 H); 6.66 (*d*, *J* = 7.8, 1 H); 7.30–7.36 (*m*, 3 H); 7.66–7.71 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): −2.49; −0.45; 31.42; 32.39; 40.23; 45.16; 49.74; 54.37; 56.73; 62.12; 91.63; 94.64; 113.83; 117.37; 119.59; 124.71; 125.76; 127.70; 129.05; 132.76; 133.75; 138.45; 143.10; 144.80; 157.68. ESI-LC-MS: 446.2 (100, $[M+1]^+$).

Data of **7b**: ^{1}H-NMR (500 MHz, $CDCl_3$): 0.37 (*s*, 3 H); 0.40 (*s*, 3 H); 0.49 (*s*, 3 H); 0.51 (*s*, 3 H); 1.21 (*dd*, *J* = 12.4, 1.5, 1 H); 2.04 (*dt*, *J* = 12.2, 4.9, 1 H); 2.29 (*s*, 3 H); 2.35 (*dd*, *J* = 12.7, 4.4, 1 H); 2.48 (*dt*, *J* = 12.7, 3.4, 1 H); 2.57 (*dd*, *J* = 18.1, 6.8, 1 H); 3.18 (*d*, *J* = 18.1, 1 H); 3.39 (*s*, 3 H); 3.48 (*d*, *J* = 6.8, 1 H); 3.90 (*s*, 3 H); 5.42 (*s*, 1 H); 5.42 (*s*, 1 H); 6.55 (*d*, *J* = 7.8, 1 H); 6.64 (*d*, *J* = 7.8, 1 H); 7.25–7.30 (*m*, 6 H); 7.42–7.46 (*m*, 2 H); 7.62–7.67 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): −3.12; −2.31; −1.81; −0.40; 30.08; 34.65; 41.94; 45.93; 51.17; 57.16;

61.50; 61.77; 96.44; 113.76; 116.70; 119.31; 119.58; 127.11; 127.45; 127.65; 128.61; 128.68; 132.57; 133.03; 133.96; 134.14; 138.91; 139.50; 142.78; 145.02; 163.41. ESI-LC-MS: 580.1 (100, $[M+1]^+$).

5-(Diphenylmethylsilyl)thebaine (=(5β)-6,7,8,14-Tetradehydro-4,5-epoxy-3,6-dimethoxy-17-methyl-5-(methyldiphenylsilyl)morphinan; **7c**). ^{1}H-NMR (500 MHz, $CDCl_3$): 0.91 (*s*, 3 H); 1.33 (*dd*, *J* = 12.7, 2.4, 1 H); 2.15 (*dt*, *J* = 12.9, 4.9, 1 H); 2.47 (*s*, 3 H); 2.50 (*d*, *J* = 5.4, 1 H); 2.85–2.95 (*m*, 2 H); 3.13 (*s*, 3 H); 3.46 (*d*, *J* = 18.1, 1 H); 3.86 (*d*, *J* = 7.8, 1 H); 3.98 (*s*, 3 H); 4.94 (*d*, *J* = 6.8, 1 H); 5.74 (*d*, *J* = 6.8, 1 H); 6.58 (*d*, *J* = 7.8, 1 H); 6.68 (*d*, *J* = 7.8, 1 H); 7.28–7.39 (*m*, 6 H); 7.65–7.69 (*m*, 2 H); 7.70–7.73 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): −1.55; 32.40; 32.80; 40.57; 45.24; 50.22; 54.21; 57.22; 62.22; 92.59; 95.12; 114.53; 116.95; 119.67; 125.48; 127.47; 127.69; 127.72; 129.16; 129.28; 133.42; 134.76; 134.82; 135.88; 137.47; 143.22; 144.77; 157.40. ESI-LC-MS: 508.3 (100, $[M+1]^+$).

7-(Diphenylmethylsilyl)thebaine (=(5α)-6,7,8,14-Tetradehydro-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(methyldiphenylsilyl)morphinan; **7d**). ^{1}H-NMR (500 MHz, $CDCl_3$): *Table 2:* additionally: 7.25–7.33 (*m*, 6 H); 7.39–7.43 (*m*, 2 H); 7.48–7.51 (*m*, 2 H). ^{13}C-NMR (125 MHz, $CDCl_3$): *Table 2*; additionally: 110.68; 127.42; 127.45; 128.74; 128.83; 134.84; 134.88; 136.91. ESI-LC-MS: 508.1 (100, $[M+1]^+$).

7-(Triphenylsilyl)thebaine (=(5α)-6,7,8,14-Tetradehydro-4,5-epoxy-3,6-dimethoxy-17-methyl-7-(triphenylsilyl)morphinan; **7e**). ^{1}H-NMR (500 MHz, $CDCl_3$): 1.79 (*dd*, *J* = 12.2, 2.0, 1 H); 2.25 (*dt*, *J* = 12.7, 4.9, 1 H); 2.39 (*s*, 3 H); 2.56 (*dd*, *J* = 18.1, 6.8, 1 H); 2.63 (*dd*, *J* = 12.7, 4.4, 1 H); 2.77 (*dt*, *J* = 12.7, 3.0, 1 H); 3.29 (*s*, 3 H); 3.47 (*d*, *J* = 6.8, 1 H); 3.50 (*d*, *J* = 18.1, 1 H); 3.86 (*s*, 3 H); 5.40 (*s*, 1 H); 5.54 (*s*, 1 H); 6.60 (*d*, *J* = 7.8, 1 H); 6.68 (*d*, *J* = 7.8, 1 H); 7.25–7.34 (*m*, 10 H); 7.48–7.52 (*m*, 5 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 28.20; 37.65; 42.12; 45.90; 46.41; 54.96; 56.71; 60.76; 86.43; 109.43; 113.52; 115.85; 119.41; 127.38; 127.69; 128.92; 131.18; 133.13; 134.72; 136.00; 142.58; 144.31; 158.60. ESI-LC-MS: 570.2 (100, $[M+1]^+$).

18-(Triphenylsilyl)benz[7,8]-6,14-endo-*ethenothebaine-3′,6′-diol (=(5α)-4,5-Epoxy-3,6-dimethoxy-17-methyl-18-(triphenylsilyl)benz[7,8]-6,14-ethenomorphinan-3′,6′-diol;* **8**). A soln. of **7e** (0.28 g, 0.5 mmol) and 1,4-benzoquinone (0.54 g, 5 mmol) in toluene (30 ml) was heated under reflux for 4 h. After cooling to r.t., the mixture was evaporated, and the residue purified by FC (AcOEt/hexane 50:50): **8** (0.34 g, 95%). Yellow foam. ^{1}H-NMR (500 MHz, $CDCl_3$): 1.78 (*dt*, *J* = 13.0, 5.2, 1 H); 1.93 (*dd*, *J* = 13.2, 2.0, 1 H); 2.42 (*dd*, *J* = 18.9, 6.4, 1 H); 2.54 (*s*, 3 H); 2.63 (*dt*, *J* = 12.7, 3.5, 1 H); 2.71 (*dd*, *J* = 12.3, 4.6, 1 H); 3.31 (*d*, *J* = 18.9, 1 H); 3.50 (*s*, 3 H); 3.71 (*s*, 3 H); 3.88 (*d*, *J* = 6.3, 1 H); 4.85 (*s*, 1 H); 5.75 (*s*, 1 H); 6.57 (*d*, *J* = 8.7, 1 H); 6.68 (*d*, *J* = 8.9, 1 H); 6.70 (*d*, *J* = 8.7, 1 H); 6.78 (*d*, *J* = 8.9, 1 H); 7.18–7.25 (*m*, 12 H); 7.30–7.35 (*m*, 3 H); 7.90 (*s*, 1 H); 12.41 (br. *s*, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 22.45; 34.14; 41.93; 45.17; 49.14; 51.49; 54.05; 56.46; 57.68; 90.84; 91.96; 114.01; 116.08; 116.69; 118.98; 119.88; 123.87; 125.44; 126.08; 127.20; 127.43; 127.57; 128.97; 129.08; 132.50; 133.98; 135.16; 135.24; 135.70; 136.07; 141.99; 142.61; 146.66; 146.89; 148.33; 149.58; 153.41. ESI-LC-MS: 678.3 (100, $[M+1]^+$).

Single-Crystal X-Ray-Diffraction Analysis of **7a** *and* **8**[1]). See *Table 3*. The crystals were grown by slow evaporation in a mixture of AcOEt/hexanes 3:1. A clear light brown crystal was mounted on a glass fiber by means of a small amount of epoxy or *Cargille* immersion oil (**7a** or **8**, resp.). Data of **7a** were collected on a *Bruker* three-circle platform diffractometer equipped with a *Smart-6000* CCD detector. The crystal was irradiated with a rotating-anode CuK_α source (λ 1.54178 Å) with incident beam *Göbel* mirrors. Data of **8** were collected on a *Bruker* three-circle platform diffractometer equipped with a *Smart-1000* CCD detector. The crystal was irradiated with graphite monochromated MoK_α radiation (λ 0.71073 Å). A *MSC-X-Stream* low-temperature device was used to keep the crystal at a constant temp. of −180° during data collection.

Data collections were performed, and the unit cells were initially refined with SMART (v5.059; *Bruker AXS, Inc.,* Madison, Wisconsin, USA). Data Reductions were performed with SAINT (v6.02A; *Bruker AXS, Inc.*) and XPREP (v6.12; *Bruker AXS, Inc.*). Corrections were applied for *Lorentz*, polarization, and absorption effects with SADABS (v2.01; *Bruker AXS, Inc.*). The structures were solved and refined with the aid of the programs in the SHELXTL-plus (v6.10) system of programs (*Bruker AXS, Inc.*). The full-matrix least-squares refinements on F^2 included atomic coordinates and anisotropic thermal parameters for all non-H-atoms. The H-atoms were included by means of a riding model. The absolute configuration of **7a** was established by making reference to an unchanging chiral center in the synthetic procedure, with a resulting *Flack* parameter of 0.16(10)

---

[1]) CCDC-254784 (**7a**) and CCDC-254785 (**8**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

Table 3. *Crystal Data and Structure Refinement for* **7a** *and* **8**

	7a	**8**
Identification code	CCDC-254784	CCDC-254785
Empirical formula	$C_{27}H_{31}NO_3Si$	$C_{43}H_{39}NO_5Si$
M_r	445.62	677.84
Temperature [K]	273(2)	93(1)
Wavelength [Å]	1.54178	0.71073
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1$
Unit-cell dimensions:		
a [Å]	8.2215(2)	10.425(2)
b [Å]	12.6160(3)	15.179(3)
c [Å]	23.1965(5)	11.299(2)
α [°]	90	90
β [°]	90	112.453(4)
γ [°]	90	90
V [Å^3]	2406.00(10)	1652.4(6)
Z	4	2
δ(calc.) [Mg/m^3]	1.230	1.362
μ [mm^{-1}]	1.081	0.122
F(000)	952	716
Crystal size [mm^3]	$0.21 \times 0.13 \times 0.03$	$0.56 \times 0.42 \times 0.32$
θ-Range for data collection [°]	3.81 – 67.48	1.95 – 28.30
Index ranges	$-9 \le h \le 7$, $-12 \le k \le 15$, $-18 \le l \le 26$	$-13 \le h \le 13$, $-20 \le k \le 19$, $-15 \le l \le 14$
Reflections collected	8290	11872
Independent reflections	3739 ($R_{int} = 0.0433$)	7225 ($R_{int} = 0.0351$)
Completeness to $\theta = 67.48°$	94.6%	97.6%
Absorption correction	semi-empirical from equivalents	semi-empirical from equivalents
Transmission (max., min.)	0.968, 0.797	0.962, 0.819
Refinement method	full-matrix least-squares on F^2	full-matrix least-squares on F^2
Data, restraints, parameters	3739, 0, 289	7225, 1, 460
Goodness-of-fit on F^2	1.051	1.034
Final R indices ($I > 2\sigma(I)$]	$R_1 = 0.0575$, $wR_2 = 0.1504$	$R_1 = 0.0410$, $wR_2 = 0.1053$
R indices (all data)	$R_1 = 0.0603$, $wR_2 = 0.1529$	$R_1 = 0.0440$, $wR_2 = 0.1072$
Absolute structure parameter	0.03(4)	0.16(10)
Largest diff. peak, hole [e · Å^{-3}]	0.363, −0.280	0.301, −0.221

[13]. The absolute configuration of **8** was established by anomalous dispersion effects in diffraction measurements on the crystal with a resulting *Flack* parameter of 0.03(4) [13].

We wish to thank the *National Institute of Drug Abuse* for financial support of this work (DA-13583), and *Noel Whittaker* for expert technical assistance.

REFERENCES

[1] L. Maat, R. H. Woudenberg, G. J. Meuzelaar, J. T. Linders, *Bioorg. Med. Chem.* **1999**, *7*, 529.
[2] A. Coop, C. L. Norton, I. Berzetei-Gurske, J. Burnside, L. Toll, S. M. Husbands, J. W. Lewis, *J. Med. Chem.* **2000**, *43*, 1852.
[3] J. W. Lewis, S. M. Husbands, *Curr. Pharm. Design* **2004**, *10*, 717.
[4] A. F. Casy, R. T. Parfitt, 'Opioid Analgesics', Plenum Press, New York and London, 1986.
[5] A. F. Casy, 'The Steric Factor in Medicinal Chemistry', Plenum Press, New York and London, 1993, p. 429 – 465.

[6] R. H. Woudenberg, L. Maat, *Recl. Trav. Chim. Pays-Bas* **1993**, *112*, 113.
[7] O. M. Soeiro, A. J. R. Da Silva, R. A. Barnes, *Chem. Pharm. Bull.* **1982**, *30*, 1998.
[8] R. M. Boden, M. Gates, S. P. Ho, P. Sundararaman, *J. Org. Chem.* **1982**, *47*, 1347.
[9] M. Gates, R. M. Boden, S. P. Ho, P. Sundararaman, *J. Org. Chem.* **1989**, *54*, 972.
[10] W. Chen, M. D. Metcalf, A. Coop, J. L. Flippen-Anderson, J. R. Deschamps, *Acta Crystallogr., Sect E* **2003**, *59*, o114.
[11] W. Chen, H. Wu, D. Bernard, M. D. Metcalf, J. R. Deschamps, J. L. Flippen-Anderson, A. D. MacKerell, A. Coop, *J. Org. Chem.* **2003**, *68*, 1329.
[12] L. P. Pratt, A. Streitwieser, *J. Org. Chem.* **2000**, *65*, 290.
[13] H. D. Flack, *Acta Crystallogr., Sect. A* **1983**, *39*, 876.

Received November 16, 2004