canamycins,[28] and virustomycin A.[29] Despite their starting units deriving from obviously different polyketide building blocks, the stereochemistry of the pentaketide moiety in 1 is the same as that in the molecules mentioned above. Further biosynthetic studies on elaiophylin (1) may also have implications for the biosyntheses of other C_2 symmetric macrodiolides, e.g., vermiculin, conglobatin, pyrenophorin or swinholide A.[30-32]

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A Novel Synthesis of the Dibenz[*b*,*f*]oxepin Ring System: 10,11-Dihydro-11-hydroxydibenz[*b*,*f*]oxepin-10(11*H*)-one

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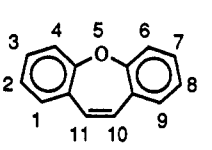
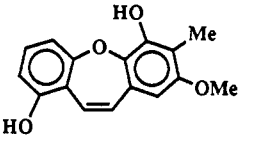
Introduction

The synthesis of dibenz[*b*,*f*]oxepin (1) was first reported in 1950 by Manske[2] and was later also synthesized by Bestmann.[3] Interestingly, the structure of pacharin (2), which was isolated from the heartwood of *Bauhinia racemosa* Lamk, has been also established as having a dibenz[*b*,*f*]oxepin skeleton.[4] In fact, derivatives of dibenz[*b*,*f*]oxepin have been found to exhibit depressant,[5] anticonvulsant,[6] analgesic,[7] antiinflammatory,[8] tranquilizing,[9] psychotropic,[10] sedative,[11] and antiestrogenic[12] properties. Our need for the identification and synthesis of new A_1 adenosine receptor ligands[13] led us to prepare functionalized dibenz[*b*,*f*]oxepins, particularly molecules that bear oxygenated functional groups at the two olefinic carbons. In this note, we report the synthesis of 10,11-dimethoxydibenz[*b*,*f*]oxepin (3) by the methylation of 10,11-dihydro-11-hydroxydibenz[*b*,*f*]oxepin-10(11*H*)-one (6). Compound 6 was itself prepared by a benzoin reaction on bis(2-formylphenyl) ether (5).



1



2

Results and Discussion

Diol 4[14] was oxidized by the Jones procedure[15] to give dialdehyde 5[16] in 47% yield (Scheme I). The benzoin condensation of 5 with potassium cyanide in dimethyl sulfoxide afforded benzoin 6 in 25% yield, together with a small amount of diketone 7.[17] It is worth noting that a longer reaction time produced more 7 and was therefore detrimental to the preparation of 6. Surprisingly, attempted formation of 3 from 6 by employing the conventional procedure gave only the methoxy ketone 8.[18] Our target molecule 3 was obtained as a colorless oil in 76% yield from 6 by treatment with sodium hydride and dimethyl sulfate in tetrahydrofuran.

The pharmacological profile of 3 is now under investigation.

Experimental Section

TLC plates were purchased from commercially available precoated Merck Kieselgel 60 F_{254} on aluminum. Column chromatography was carried out using Merck silica gel (70–230 mesh). All evaporations were performed under reduced pressure with a rotary evaporator. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ at 250 and 62.5 MHz, respectively. Melting points were recorded on a hot-stage microscope and are uncorrected.

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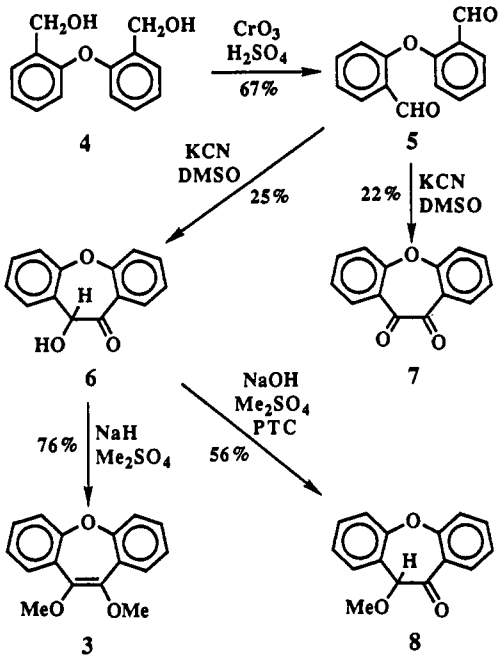
Scheme I



Bis(2-formylphenyl) Ether (5). A solution of CrO_3 (10 g, 0.1 mol) in 2 N H_2SO_4 (200 mL) was added dropwise over 30 min to a solution of compound 4[14a] (11.5 g, 50 mmol) in acetone (200 mL) at 0 °C under N_2. After the addition, the mixture was stirred for a further 15 min and was then quenched by addition of 2-propanol (15 mL). After 15 min, solid $NaHCO_3$ (14 g) was added, and the mixture was filtered through a sintered-glass filter. The filtrate was concentrated under vacuum and the residue was chromatographed on a silica gel column (100 g, hexanes/ethyl acetate 4:1) to give compound 5 (7.5 g, 67%), mp 77–77.5 °C [lit.[16b] mp 74 °C]: ^{1}H-NMR δ 6.96 (d, J = 8.3 Hz, 2 H), 7.31 (m, 2 H), 7.59 (m, 2 H), 8.00 (dd, J_1 = 7.8 Hz, J_2 = 1.8 Hz, 2 H), 10.51 (s, 2 H); ^{13}C-NMR δ 119.02 (CH), 124.43 (CH), 127.37 (C), 129.21 (CH), 135.78 (CH), 158.73 (C), 188.24 (CH); MS (EI) m/e 226 (M^+). Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.69; H, 4.51.

10,11-Dihydro-11-hydroxydibenz[*b*,*f*]oxepin-10(11*H*)-one (6) and 10,11-Dihydrodibenz[*b*,*f*]oxepin-10,11-dione (7). To a solution of compound 5 (1.78 g, 7.5 mmol) in DMSO (3 mL) was added KCN (0.2 g, 3 mmol) under N_2. The mixture was stirred at rt for 4 h and was then filtered through a silica gel column (50 g, 70–230 mesh, hexanes/ethyl acetate 3:2) to give a crude mixture of 6 and 7 after evaporation. The crude mixture of 6 and 7 was purified by chromatography on a silica gel column (50 g, hexanes/ethyl acetate 4:1) to afford 6 (0.42 g, 25%) and 7 (0.12 g, 6%), respectively. However, the yields of 6 and 7 were 4% and 22%, respectively, when the reaction was carried out for 20 h and 7.5 mmol of 5 and 6 mmol of KCN were used. Compound 6: yellowish solid, mp 79–81 °C. Compound 7: yellowish solid, mp 114–116 °C [lit.[17a] mp 119 °C].

^{1}H-NMR (6): δ 5.84 (s, 1 H), 7.15 (m, 1 H), 7.22 (m, 3 H), 7.36 (m, 1 H), 7.52 (m, 1 H), 7.3 (m, 1 H), 8.09 (m, 1 H). ^{13}C-NMR (6): δ 75.37 (CH), 120.12 (CH), 121.71 (CH), 123.50 (C), 124.09 (CH), 125.35 (CH), 126.54 (CH), 128.86 (CH), 130.24 (C), 130.82 (CH), 135.88 (CH), 154.32 (C), 160.52 (C), 191.68 (C). MS (EI): m/e 226 (M^+) (6). Anal. Calcd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46. Found: C, 74.28; H, 4.37.

^{1}H-NMR (7): δ 7.32 (m, 2 H), 7.42 (d, J = 8.2 Hz, 2 H), 7.66 (ABX, J_1 = 8.2 Hz, J_2 = 7.9 Hz, J_3 = 1.7 Hz, 2 H), 7.99 (dd, J_1 = 7.9 Hz, J_2 = 1.7 Hz, 2 H). ^{13}C-NMR (7): δ 121.72 (CH), 125.60 (CH), 126.32 (C), 131.80 (CH), 135.83 (CH), 156.97 (C), 186.53 (C). MS (EI): m/e 224 (M^+) (7). Anal. Calcd for $C_{14}H_8O_3$: C, 74.99; H, 3.59. Found: C, 74.75; H, 3.51.

10,11-Dihydro-11-methoxydibenz[*b*,*f*]oxepin-10(11*H*)-one (8). To a solution of 6 (226 mg, 1 mmol) in THF (5 mL) were added methyltrioctylammonium chloride (2 drops) and a solution of NaOH (170 mg, 4 mmol) in water (0.7 mL) under N_2. To the resulting mixture was added dimethyl sulfate (285 μL, 3 mmol). The mixture was stirred at rt under N_2 for 20 h. $CHCl_3$ (30 mL) was added and the organic layer was washed with water (2 × 5 mL) and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was chromatographed on a silica gel column (30 g, hexanes/ethyl acetate 2:1) to give 8 (136 mg, 56%), mp 179–181 °C: ^{1}H-NMR δ 3.59 (s, 3 H), 5.33 (d, J = 1 Hz, 1 H), 7.16 (m, 4 H), 7.36 (m, 2 H), 7.49 (dd, J_1 = 7.3 Hz, J_2 = 0.8 Hz, 2 H); ^{13}C-NMR δ 53.78 (CH_3), 70.14 (CH), 116.90 (CH), 122.15 (C), 123.49 (CH), 126.76 (CH), 129.95 (CH), 150.50 (C), 174.98 (C); MS (EI) m/e 240 (M^+). Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 74.21; H, 5.26.

10,11-Dimethoxydibenz[*b*,*f*]oxepin (3). To a solution of compound 6 (226 mg, 1 mmol) in THF (5 mL) were added NaH (72 mg, 3 mmol) and dimethyl sulfate (315 mg, 0.24 mL, 2.5 mmol). The mixture was stirred at rt under N_2 for 4 h. The mixture was then diluted with $CHCl_3$ (30 mL). The organic layer was washed with water (2 × 5 mL) and dried (Na_2SO_4). The solvent was removed under vacuum and the residue was chromatographed on a silica gel column (50 g, hexanes/ethyl acetate 4:1) to afford compound 3 as an oil (195 mg, 76%): ^{1}H-NMR δ 3.80 (s, 6 H), 7.15 (m, 4 H), 7.30 (ABX, J_1 = 7.95 Hz, J_2 = 7.66 Hz, J_3 = 1.81 Hz, 2 H), 7.50 (dd, J_1 = 7.66 Hz, J_2 = 1.81 Hz, 2 H); ^{13}C-NMR δ 60.26 (CH_3), 120.89 (CH), 124.87 (CH), 126.94 (CH), 127.5 (C), 129.73 (CH), 143.98 (C), 157.54 (C); MS (EI) m/e 254 (M^+). Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55. Found: C, 75.15; H, 5.60.

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Registry No. 3, 141511-32-2; 4, 10038-40-1; 5, 49590-51-4; 6, 141511-33-3; 7, 68978-15-4; 8, 141511-34-4.

Supplementary Material Available: ^{1}H- and ^{13}C-NMR spectra of 3, 11, 12, and 13 (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Selectivity in Radical-Cation Diels–Alder Reactions of Indole and Electron-Rich Dienes: A Semiempirical Approach

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Introduction

The use of cation radicals in organic chemistry is a field of increasing interest. During the last decade, particularly the radical-cation Diels–Alder reaction[1] has been the subject of many mechanistic/theoretical[2] and preparative investigations.[3] The typical features of this reaction are the increase of reaction rates by several orders of magnitude over these of the neutral reaction coupled with a high regio- and chemoselectivity. Therefore it is a promising tool for organic synthesis. The methods of computational chemistry and MO theory have been highly successful in studies of normal Diels–Alder reactions, so it is not astonishing that for radical-cation cycloadditions, quantum

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