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A SHORT SYNTHESIS OF (±)-3′,6′-EPOXYCYCLOAURAPTEN

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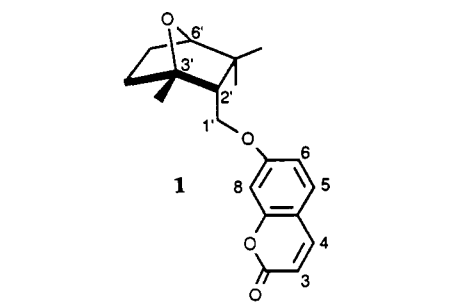
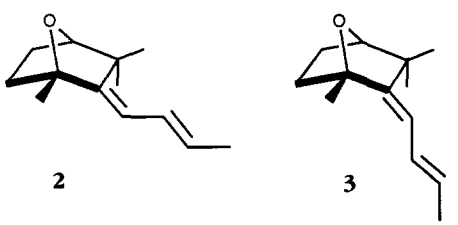
ABSTRACT.—(±)-3′,6′-Epoxycycloaurapten [**1**] was synthesized in eight steps and 14% overall yield from 2-methylfuran. The Diels-Alder reaction of 2-methylfuran with 2-chloroacrylonitrile was used to synthesize 1,3,3-trimethyl-7-oxabicyclo[2.2.1]heptan-2-one [**4**] in four steps as part of a synthesis of (±)-2,5-epoxy-6(*E*),8(*E*)-megastigmadiene [**2**] as reported previously. Ketone **4** has now been converted into the corresponding methylene derivative **5** via a Wittig reaction. Hydroboration-oxidation followed by formation of the mesylate derivative and displacement with the potassium salt of 7-hydroxycoumarin gave (±)-3′,6′-epoxycycloaurapten [**1**].

The 1,3,3-trimethyl-7-oxabicyclo [2.2.1]heptane system is found as a major component of a number of interesting plant secondary metabolites. Among these are 3′,6′-epoxycycloaurapten [**1**] (1) and 2,5-epoxymegastigma-6(*E*),8(*E*)-diene [**2**] and its 6(*Z*) isomer **3** (2). Although previous syntheses of **1–3** have left creation of the oxygen bridge of the 7-oxabicyclo[2.2.1]heptane moiety as a late step in the synthesis, contributing to low yields and mixtures of products (1, 3–5), our recent synthesis of **2** employed the intermolecular Diels-Alder reaction of 2-methylfuran and 2-chloroacrylonitrile to create the oxygen bridge in the initial step (6). In this synthesis, 1,3,3-trimethyl-7-oxabicyclo [2.2.1]heptan-2-one [**4**] served as a key intermediate, having been prepared in four steps and 51% yield from 2-methylfuran. Clearly, **4** contains the functionality (i.e., three correctly placed methyl groups, the oxygen bridge, and a ketone moiety which may be used for addition of substituents at C-2) required to prepare other natural products containing this monoterpenoid system. We now report the synthesis of one such natural product, (±)-3′,6′-epoxycycloaurapten [**1**].



1



2 **3**

In order to convert **4** into **1**, it was necessary to carry out a one-carbon homologation with subsequent functionalization of the added carbon. In our synthesis of **2** (6), addition of the side chain at C-2 was envisioned originally as a Wittig reaction. However, addition of the side chain required for **2** via a Wittig reaction was impossible due to the steric hindrance around the carbonyl carbon. This was in sharp contrast to the reaction of **4** with the ylide formed from methyltriphenylphosphonium bromide and *n*-butyllithium which gave 2-methylenyl-1,3,3-trimethyl-7-oxabicyclo[2.2.1] heptane [**5**] in 80% yield. This result was ideal for a synthesis of **1**.

Initially, an attempt was made to convert **5** directly into **7** via an anti-Markovnikov addition of hydrogen bromide. However, the conditions for this reaction were too severe and resulted in destruction of the oxabicycloheptane nucleus. Accordingly, milder conditions were sought which would result in

1. LiI, 0°, 14 days
2. H2/Pd-C/EtOAc
3. KOH/t-BuOH-H2O
4. 2 eq MeI/t-BuO−
(C6H5)3P+CH3 I−
n-BuLi/THF
1) BH3-THF
2) H2O2/OH−
CBr4/(C6H5)3P
or
MsCl/pyridine
K2CO3/Me2CO
4
5
7 R=Br
8 R=OSO2CH3
6a R1=H, R2=CH2OH
6b R1=CH2OH, R2=H
1

SCHEME 1

an overall anti-Markovnikov addition to the double bond. The optimum reaction proved to be hydroboration-oxidation. Treatment of **5** with BH_3-THF complex followed by basic H_2O_2 gave the primary alcohol as a mixture of diastereomers **6a** and **6b**, with one isomer predominating to the extent of greater than 9:1 by gc-ms. The major isomer was assumed to be the desired endo isomer **6a**, resulting from addition to the less hindered beta (exo) face of **5**. However, this mixture was difficult to separate on a preparative scale without significant loss of material and, as a result, was carried on as a mixture to the next step.

Bromide **7** was obtained, as a mixture of isomers, from **6a** + **6b** by bromination with carbon tetrabromide/triphenylphosphine (7) in approximately 76% yield. Unfortunately, this derivative was unstable, even at 0°, and purification was difficult. This instability was also a problem in using **7** for the next reaction, a substitution reaction with the sodium salt of 7-hydroxycoumarin. Attempts to carry out this displacement reaction led to some of the desired product **1** (ca. 11%), but the elevated temperatures required resulted in elimination to return **5** as well as decomposition of both products and **7**.

In view of the instability of **7** and its tendency to undergo elimination rather than substitution, another, more stable, derivative was required. After considering and discarding several alternatives, preparation of the mesylate derivative **8** was investigated. Initially, two products were obtained and the major product was separated by cc to give the mesylate **8** in 89% yield. The minor derivative was not isolated but is presumably the other isomer (the C-2 enantiomer). Mesylate **8** was indeed more stable than bromide **7** but would also decompose after several hours at room temperature. The stereochemistry of **8** was confirmed by an nOe experiment in which irradiation of the methyl singlet at δ 1.07 due to the 3β methyl group resulted in a 2–3% increase in the intensity of the H-2 multiplet at δ 1.67. Irradiation at δ 1.67 gave a 2–3% increase in the methyl singlet at δ 1.07. No change was seen in the intensity of the methyl singlet at δ 0.88, which was assigned to the 3α methyl group (this assignment is based upon the expected shielding of the 3α methyl group by the bicyclic ring). Irradiation of the singlet at δ 0.88 did, however, result in a 2–5% enhancement of the two doublets of doublets at δ 4.08 and δ 4.17 due to the C-9 diastereotopic protons. Irradiation of each of these sets of resonances also resulted in enhancement of the δ 0.88 singlet but not the δ 1.07 singlet. Thus, the major isomer from hydroboration-oxidation of **5** was found to have the desired stereochemistry for the synthesis of **1**.

Displacement of the mesylate group of **8** with the sodium salt of 7-hydroxycoumarin in DMF was attempted using the procedure employed by Coates and Melvin (4) to synthesize a precursor in their synthesis of **1**. However, it was necessary to raise the temperature to reflux in order to achieve any significant displacement of the mesylate and, under these conditions, elimination was a major competing path; the yield of **1** was only 28%. A better procedure employed the potassium salt of 7-hydroxycoumarin in refluxing Me_2CO (8). The elimination reaction, while still a major competing reaction, was reduced and a 40% yield of racemic **1** was obtained after cc. The ^{1}H-nmr spectrum of this sample of **1** was identical to a ^{1}H-nmr spectrum of **1** provided by Dr. F. Rouessac. Longer reaction times or lower temperatures did not enhance this yield, presumably because the carbon bearing the mesylate is sterically hindered by the bicyclic ring system and approach by the bulky nucleophile is difficult, allowing elimination to predominate. However, this route did achieve an overall 14% yield of (±)-3′,6′-epoxycycloaurapten [**1**] in 8 steps from 2-methylfuran and again showed the usefulness of the inter-

molecular Diels-Alder reaction of furans in the synthesis of natural products containing a 7-oxabicyclo[2.2.1]heptane system.

EXPERIMENTAL

GENERAL EXPERIMENTAL PROCEDURES.—Ir spectra were recorded on a Perkin-Elmer Model 1600 Ft-ir spectrometer. ^{1}H- and ^{13}C-nmr spectra were obtained using a GE QE-300 nmr at 300 MHz and 75.6 MHz, respectively, with TMS as an internal standard. Mass spectra were recorded using a Hewlett-Packard Model 5988A gc/ms coupled with a Hewlett-Packard 59970 MS Chemstation. Injection port and column oven temperatures were 225° and 250°, respectively. High resolution mass spectra were obtained at the Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska, Lincoln, Nebraska. Melting points were obtained on a Fischer-Johns melting point apparatus and are uncorrected. Si gel refers to Si gel 60 G (EM Labs). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

1,3,3-TRIMETHYL-2-METHYLENYL-7-OXABICYCLO[2.2.1]HEPTANE [**5**].—To a solution of methyltriphenylphosphonium iodide (10.35 g, 25.6 mmol) in THF (100 ml) under N_2 at 0° was added 17 ml of 1.6 M *n*-butyllithium in hexane. The yellow solution was allowed to warm to room temperature over 4 h, at which point the solution turned red. To this solution was added a solution of **4** [3.48 g, 22.3 mmol, prepared as in DiFazio *et al.* (6)] in THF (25 ml), and the resulting mixture was stirred for 48 h. A white precipitate was removed by gravity filtration to give a light-orange-colored filtrate which was dried over anhydrous $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by distillation in a Kugelrohr apparatus to give **5** as a clear colorless liquid, 2.74 g (81%): bp 35° (0.2 mm); ir (film) 3050, 2950, 2850, 1660, 1445, 1180 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 4.63 (s, 1H, H-8), 4.51 (s, 1H, H-8), 3.89 (d, J = 5.1 Hz, 1H, H-4), 1.79 (m, 1H, H-6), 1.67 (m, 1H, H-5), 1.38–1.52 (m, 2H, H-5, -6), 1.42 (s, 3H, 1-Me), 1.03 (s, 3H, 3-Me), 1.01 (s, 3H, 3-Me); ^{13}C nmr ($CDCl_3$) 18.30 q (1-Me), 23.75 q (3-Me), 25.84 q (3-Me), 28.66 t (C-5), 35.65 (C-6), 45.83 s (C-3), 84.46 d (C-4), 86.41 s (C-1), 97.96 t (C-8), 100.31 s (C-2); eims *m/z* (rel. int.) [M]$^+$ 152 (29), 137 (29), 123 (26), 109 (100), 93 (26), 81 (32), 69 (34), 55 (11).

2-(HYDROXYMETHYL)-1,3,3-TRIMETHYL-7-OXABICYCLO[2.2.1]HEPTANE [**6**].—A solution of borane-THF complex (10 ml, 16 mmol) was added dropwise to a solution of **5** (2.29 g, 15.1 mmol) in 100 ml of anhydrous Et_2O at 0° under N_2. The mixture was allowed to warm to room temperature and stirred for 5 h. The solution was cooled to 0°, and 1 N NaOH (10 ml) and 30% H_2O_2 (10 ml) were added, leading to the evolution of gas. The solution was allowed to warm to room temperature over 6 h and was extracted with Et_2O (4 × 40 ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resulting yellow oil was purified by Kugelrohr distillation to give **6** as a clear, colorless oil, 2.48 g (97%): bp 73°; ir (film) 3400 (br), 2960, 1430, 1375, 1080 cm^{-1}; ^{1}H nmr (major isomer) ($CDCl_3$) δ 3.77 (d, 1H, J = 4.89 Hz, H-4), 3.64 (dd, 2H, J = 6.83 Hz, H_2-8), 1.8–1.3 (m, 5H, H-2, H_2-5, H_2-6), 1.34 (s, 3H, 1-Me), 1.04 (s, 3H, 3-Me), 1.00 (s, 3H, 3-Me); eims *m/z* (rel. int.) [M]$^+$ 170 (10), 155 (35), 139 (39), 121 (43), 109 (71), 96 (67), 82 (71), 79 (36), 67 (50), 55 (43).

2-(BROMOMETHYL)-1,3,3-TRIMETHYL-7-OXABICYCLO[2.2.1]HEPTANE [**7**].—To a solution of carbon tetrabromide (5.11 g, 15.4 mmol) in 25 ml of freshly distilled CH_2Cl_2 at 25° was added a solution of triphenylphosphine (4.50 g, 17.2 mmol) in 50 ml of CH_2Cl_2. Alcohol **6** was dissolved in 10 ml of CH_2Cl_2 and added dropwise. The solution was stirred for 5 h at 25°, then washed successively with H_2O (40 ml) and saturated aqueous NaCl (2 × 40 ml) and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to give a yellow oil which was purified by cc over Si gel eluting with $CHCl_3$ to give **7** as a yellow oil (2.18 g, 76%): ir ($CHCl_3$) 2928, 2856, 1456, 1375, 1363 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 3.79 (d, 1H, H-4), 3.25 (m, 2H, CH_2Br), 2.22 (m, 1H, H-2), 1.86–1.43 (m, 4H, H_2-5, -6), 1.42 (s, 3H, 1-Me), 1.08 (s, 6H, 3-Me).

1,3,3-TRIMETHYL-2-(METHANESULFONYLMETHYL)-7-OXABICYCLO[2.2.1]HEPTANE [**8**].—To a solution of **6** (4.78 g, 28.1 mmol) in dry pyridine (75 ml) was added Na metal (0.664 g, 28.9 mmol) at 0° under N_2. The mixture was allowed to stir for 2 h, and then 3 ml of methanesulfonyl chloride (38.8 mmol) was added. The solution was stirred for 1 h at 0° and then warmed to room temperature over 12 h. The white precipitate was removed by vacuum filtration and washed with Et_2O (4 × 30 ml). The dark yellow filtrate was washed with H_2O (40 ml), 1 N $NaHCO_3$ (2 × 30 ml), and saturated aqueous $CuSO_4$ (5 × 50 ml), and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to yield an orange oil that was purified by cc over Si gel eluted with CH_2Cl_2 to give **8** as a light yellow oil, 6.19 g (89%): ir (film) 2950, 2880, 1460, 1345, 1170 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ 4.12 (dd, 2H, J = 13.69, 2.93 Hz, H-8), 3.85 (d, 1H, J = 3.9 Hz, H-4), 2.95 (s, 3H, $MeSO_2$), 1.67 (m, 1H, H-2), 1.7–1.5 (m, 4H, H_2-5, -6), 1.42 (s, 3H, 1-Me), 1.07 (s, 3H, 3β-Me), 0.88 (s, 3H, 3α-Me); ^{13}C nmr ($CDCl_3$) 19.07 q (3-Me),

21.67 q (1-Me), 26.33 t (C-6), 29.37 t (C-5), 31.75 q (3-Me), 37.38 q ($MeSO_2$), 42.48 s (C-3), 55.16 d (C-2), 68.27 t (C-8), 85.82 d (C-4), 86.58 ppm s (C-1); eims *m/z* (rel. int.) $[M]^+$ 248 (3), 233 (7), 169 (11), 153 (20), 137 (100), 123 (22), 109 (82), 95 (56), 79 (68), 67 (45), 55 (30).

(±)-3′,6′-EPOXYCYCLOAURAPTEN [**1**].—To a solution of 7-hydroxycoumarin (1.77 g, 10.9 mmol) in dry Me_2CO (100 ml) was added anhydrous K_2CO_3 (1.94 g) at 25° under N_2. After 4 h, a solution of **8** (2.19 g, 8.94 mmol) in Me_2CO (10 ml) was added dropwise to the yellow mixture. The solution was heated at reflux for 30 h and cooled, and the K_2CO_3 was removed by filtration. The Me_2CO was removed in vacuo, and the residue was dissolved in Et_2O (100 ml). The Et_2O solution was washed successively with 1 N NaOH (2 × 50 ml), saturated NaCl (2 × 50 ml), and H_2O (3 × 50 ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo to give a yellow oil which was purified by cc over Si gel eluted with $CHCl_3$-MeOH (95:5) to give **1**, 1.14 g (40%): mp 153–155° [Et_2O/pentane, lit. (1) 155–156°]; ir 3050, 3960, 1720, 1600, 1550, 1190 cm^{-1}; ^1H nmr ($CDCl_3$) δ 7.64 (d, 1H, J = 9.5 Hz, H-4), 7.37 (d, 1H, J = 9.3 Hz, H-5), 6.82 (m, 2H, H-6, -8), 6.25 (d, 1H, J = 9.5 Hz, H-3), 4.00 (dd, 1H, J = 8, 9 Hz, H-1′), 3.96 (dd, 1H, J = 8, 9 Hz, H-1′), 3.82 (d, 1H, J = 5.1 Hz, H-6′), 1.98 (m, 1H, H-2′), 1.85–1.45 (m, 4H, H_2-4′, -5′), 1.40 (s, 3H, 3′-Me), 1.16 (s, 3H, 7′β-Me), 1.08 (s, 3H, 7′α-Me); ^{13}C nmr ($CDCl_3$) 19.48 q (7′-Me), 20.04 q (7′-Me), 23.49 t (C-4′), 26.92 t (C-5′), 33.39 q (3′-Me), 43.11 s (C-7′), 51.70 d (C-2′), 66.05 t (C-1′), 86.94 d (C-6′), 87.97 s (C-3′), 104.40 d (C-6), 117.54 d (C-3), 118.24 s (C-4a), 120.02 d (C-5), 135.25 d (C-4), 135.87 d (C-8), 151.54 s (C-7), 151.7 s (C-8a), 172.61 s (C-2); hreims *m/z* $[M]^+$ 314.1519; calcd for $C_{19}H_{22}O_4$, 314.1518. *Anal.* calcd. for $C_{19}H_{22}O_4$: C 72.58, H 7.05; found C 72.18, H 7.08.

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LITERATURE CITED

1. R. Bohlmann, C. Zdero, and H. Kapteyn, *Liebigs Ann. Chem.*, **717**, 186 (1968).
2. R. Kaiser and D. Lamparsky, *Helv. Chim. Acta*, **61**, 373 (1978).
3. K. Mori and H. Tamura, *Tetrahedron*, **42**, 2643 (1986).
4. R.M. Coates and L.S. Melvin Jr., *Tetrahedron*, **26**, 5699 (1970).
5. M. Aziz and F. Rouessac, *Tetrahedron*, **44**, 101 (1988).
6. M.P. DiFazio, W.A. Wallace, and A.T. Sneden, *Heterocycles*, **29**, 2393 (1989).
7. J. Hooz and S.S.H. Gilani, *Can. J. Chem.*, **46**, 86 (1968).
8. P.G. Baraldi, M. Quarneri, S. Manfredini, D. Simoni, J. Balzarini, and E. De Clercq, *J. Med. Chem.*, **32**, 284 (1989).

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