and the organic phase was washed with water, dried, and evaporated to leave solid **26** which was recrystallized from $CHCl_3$/MeOH to give 2.8 g (62%) of pure **26**: mp 91–92 °C; IR 1670, 1240, 1040 cm^{-1}; NMR δ 1.33 (t, J = 7 Hz, 3, CH_2CH_3), 3.77, 3.87, 3.90 (3 s, 3 × 3, OCH_3), 4.13 (s, 2, $ArCH_2$), 4.43 (q, J = 7 Hz, 2, CH_2CH_3), 6.85, 7.00, 7.62, 7.77 (AB q, 2, 5-H and 6-H), 6.77, 6.92, 7.10, 7.25 (AA'BB' q, 4, 2'-H, 3'-H, 5'-H, and 6'-H). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.04; H, 6.14. Found: C, 67.27; H, 6.30.

2'-(Ethoxycarbonyl)-4,3',4'-trimethoxydeoxybenzoin (27) was obtained in 57% yield from **11** by the same procedure: mp 81–82 °C; IR 1720, 1670, 1260, 830 cm^{-1}; NMR δ 1.26 (t, J = 7 Hz, 3, CH_2CH_3), 3.87, 3.90 (superimposed s, 9, OCH_3), 4.23 (s, 2, $ArCH_2$), 4.28 (q, J = 7 Hz, 2, CH_2CH_3), 6.87, 7.02, 7.96, 8.11 (AA'BB' q, 4, 2-H, 3-H, 5-H, and 6-H, 6.95 (s, 2, 5'-H and 6'-H). Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.04; H, 6.14. Found: C, 66.98; H, 6.31.

3-(3,4-Dimethoxybenzylidene)-6,7-dimethoxyphthalide (28) and 3-(3,4-Dimethoxyphenyl)-7,8-dimethoxyisocoumarin (29). Compound **12** (19 g, 52.7 mmol) was lithiated according to the general procedure except that the ice bath was removed after the addition of *n*-butyllitium; solid CO_2 was used as the electrophile. The aqueous phase from the hydrolyzed reaction mixture was washed with ether, made acidic by adding concentrated HCl, and extracted with CH_2Cl_2. The organic extract was dried and evaporated. The residue was suspended in 100% H_3PO_4 (150 mL) and the mixture heated on a steam bath for 1 h. The resulting solution was poured into water, the oil which separated was taken up in $CHCl_3$, and the organic solution was washed with diluted NaOH, dried, and evaporated to give a thick oil which solidified by trituration with EtOH. This material (13.5 g, 74.9%) turned out to be a mixture of **28** and **29** in the approximate ratio of 7:3. Compound **28** was obtained in a pure form by crystallization of the mixture from $CHCl_3$/EtOH: mp 170–172 °C; IR 1770 (five-membered lactone), 1500, 1260, 1010, 800 cm^{-1}; NMR δ 3.88, 3.90, 3.92, 4.15 (4 s, 4 × 3, OCH_3), 6.15 (s, 1, vinylic), 6.75, 6.88, 7.03–7.37 (m, 5, aromatic). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.30; H, 5.30. By refluxing **28** with an excess of sodium methoxide in MeOH, a deep red solution was obtained, from which 2-(3,4-dimethoxyphenyl)-6,7-dimethoxyindan-1,3-dione separated as a solid [mp 189–191 °C (lit.[8] mp 190–191 °C)] on treatment with diluted HCl. The isocoumarin **29** was obtained in a pure form by chromatography (silica gel, eluant $CHCl_3$) and recrystallization from $CHCl_3$/MeOH: mp 160 °C; IR 1720 (six-membered lactone), 1270, 1250, 1010, 800 cm^{-1}; NMR δ 3.90, 3.93, 3.96 (partially superimposed s, 12, OCH_3), 6.70 (s, 1, vinylic), 6.83–7.53 (m, 5, aromatic). Anal. Calcd for $C_{19}H_{18}O_6$: C, 66.66; H, 5.30. Found: C, 66.35; H, 5.46.

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Registry No. 1, 2878-54-8; **2**, 2878-55-9; **3**, 3840-28-6; **4**, 86633-25-2; **5**, 59276-33-4; **6**, 59259-90-4; **7**, 85452-72-8; **8**, 86633-26-3; **9**, 86633-27-4; **10**, 86633-28-5; **11**, 86633-29-6; **12**, 86633-30-9; **15**, 569-31-3; **16**, 4741-65-5; **17**, 86633-31-0; **18**, 86633-32-1; **19**, 86633-33-2; **20**, 65495-31-0; **21**, 75267-19-5; **22**, 519-05-1; **23**, 58343-48-9; **24**, 86633-34-3; **25**, 86633-35-4; **26**, 86633-36-5; **27**, 86633-37-6; **28**, 86633-38-7; **29**, 86633-39-8; ethyl vinyl ether, 109-92-2; 3,4-dimethoxybenzyl alcohol, 93-03-8; 3,4-(methylenedioxy)benzyl alcohol, 495-76-1; 4-methoxybenzyl alcohol, 105-13-5; 3,4-dimethoxybenzaldehyde, 120-14-9; 3,4-(methylenedioxy)benzaldehyde, 120-57-0; (3,4-dimethoxyphenyl)acetaldehyde, 5703-21-9; [3,4-(methylenedioxy)phenyl]-acetaldehyde, 6543-34-6; 2-(3,4-dimethoxyphenyl)ethyl alcohol, 7417-21-2; (4-methoxyphenyl)acetic acid, 104-01-8; 1,2-dimethoxybenzene, 91-16-7; 3,4,4'-trimethoxydeoxybenzoin, 4927-54-2; ethylene glycol, 107-21-1; (3,4-dimethoxyphenyl)acetic acid, 93-40-3; methoxybenzene, 100-66-3; 3,3',4'-trimethoxydeoxybenzoin, 4927-53-1; 3,4,3',4'-tetramethoxydeoxybenzoin, 4927-55-3; 2-(3,4-dimethoxyphenyl)-6,7-dimethoxyindan-1,3-dione, 1641-12-9.

Studies in the 2,4-Disubstituted Adamantanes. Preparation and Reactivity of Pure Epimeric 4-Hydroxy- and 4-Methoxyadamantan-2-ones[1]

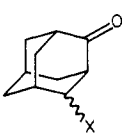
James G. Henkel* and Joni H. Spector

Section of Medicinal Chemistry and Pharmacognosy, School of Pharmacy, U-92, The University of Connecticut, Storrs, Connecticut 06268

Received January 27, 1983

Facile syntheses of the epimerically pure 4(e)- and 4(a)-hydroxyadamantan-2-ones (**7** and **8**), as well as the corresponding 4(e)- and 4(a)-methoxyadamantan-2-ones (**9** and **10**), are reported. Although **7** and **8** are both acid and base labile, the corresponding ethylene ketals are stable to base and serve as useful intermediates for both syntheses. The acid-catalyzed epimerization of **7** and **8** was studied and found to occur under relatively mild conditions, while the corresponding methoxy derivatives were found to be inert to the same acidic conditions. This approach offers a convenient route to protected 4-substituted adamantan-2-ones that are configurationally stable to further synthetic transformations.

The chemistry of bridge-substituted adamantanes has stimulated considerable investigative effort in recent years.[2-4] One family within this series that has been particularly rich in its yield of chemical insight is the 4-substituted adamantan-2-one system, **1**. The defined geometry of this series is ideally suited for studies of a variety of intramolecular mechanistic processes[5,6] as well



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as biological[7] interactions. Of particular interest is the strong influence of the stereochemistry of the 4-substituent on chemical reactivity. When X is equatorial to the cyclohexanone ring portion of the molecule, π-route-related fragmentation reactions are often observed. Cogent ex-

(1) Based in part on the M.S. Thesis of Joni H. Spector, University of Connecticut, 1982.
(2) For an extensive review see: Fort, R. C., Jr. "Adamantane, the Chemistry of Diamond Molecules"; Dekker: New York, 1976.
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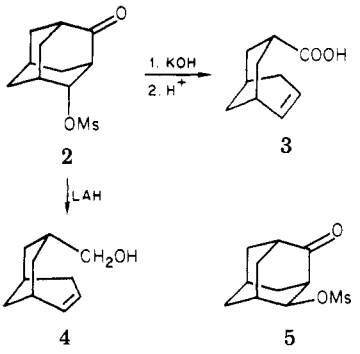
Scheme I

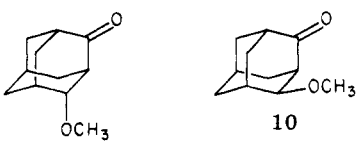


amples of this unusual reactivity include the ring-opening reaction of 4(e)-(methylsulfonoxy)adamantan-2-one (**2**) with base to give carboxylic acid **3**[8] and the reductive fragmentation of **2** to give alcohol **4**.[6] The decomposition of the presumed tetrahedral intermediate resulting from attack on the carbonyl group of **2** likely follows a Grob-type pathway.[9] The 4(a)-epimer **5** is not known to undergo such fragmentations.[6] (See Scheme I.)

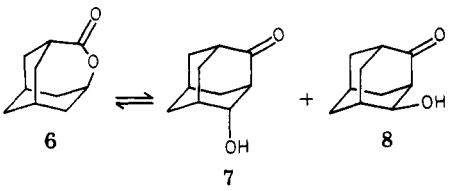
There are several lines of evidence that support the greater thermodynamic stability of the 4(a)-substituted derivatives of **1** over the 4(e)-epimers. For example, treatment of either **2** or **5** with hot methanesulfonic acid for 1 h affords a 1:6 equilibrium mixture of **2** and **5**.[10] A second example of a π-route equilibrium process favoring the 4(a)-epimer is the rearrangement of lactone **6** in 50% H_2SO_4,[10] conditions under which a 1:1:5 equilibrium mixture of **6**, **7**, and **8**, respectively, is formed. (See Scheme II.)

While some 4(e)-substituted products are readily obtainable (e.g., **2**), placement of other more stable substituents at the 4(e)-position has not been a straightforward process. Under conditions sufficiently vigorous to form **7** and **8** or their derivatives by rearrangement, thermodynamic rather than kinetic product control is in effect and the more stable 4(a)-product has predominated in all previous cases.[6,10-13] The method of choice for the synthesis of a mixture of the respective 4(e)- and 4(a)-hydroxy ketones **7** and **8** appears to be the π-route ring closure of **3** as originally reported by Faulkner and McKervey[10] and subsequently modified by Numan and Wynberg.[6] By the use of the latter procedure (Ac_2O, C_6H_6, and BF_3 followed by KOH), **3** can be converted in 85% yield into a ca. 20:80 mixture of **7** and **8**, respectively. Again, the product composition of this reaction reflects thermodynamic product control, and thus quantities of **7** are difficult to obtain.

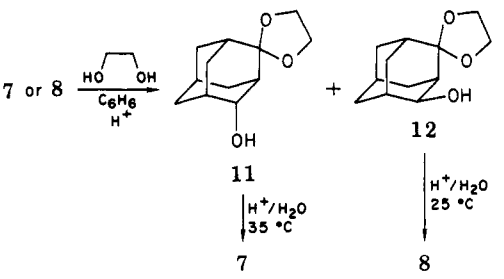
As part of another project, we required a quantity of 4(e)-methoxyadamantan-2-one, **9**, free of the 4(a)-epimer **10**. While **10** has been well characterized,[14] **9** has been



Scheme II



Scheme III



much more elusive. Although it has been recently reported,[15] a subsequent report has indicated that its preparation is not straightforward.[16] Treatment of either **7** or **8** with excess NaH and CH_3I returns only **10** along with minor amounts of reduced products. An entirely satisfactory explanation of this unusual behavior has not yet appeared. We have thus undertaken a study of the chemical stability and reactivity of **7** and **8** as well as **9** and **10** and herein report the results. We also wish to report a synthesis of each epimer free of the other, for both the hydroxy and the methoxy series.

Results and Discussion

Repeating the synthesis of **7** and **8** by the method of Numan and Wynberg,[6] we could not fully separate the epimers on preparative HPLC under the stated conditions (Waters Prep/LC 500 chromatograph, silica cartridge, 4:1 hexane–acetone, flow rate 250 mL/min). Modification of these conditions did not improve the results. While the trailing major (axial) isomer **8** could be readily isolated, the leading minor (equatorial) isomer **7** continually appeared as a shoulder on **8**. It could not be isolated free of contamination by **8**, even by peak shaving and recycling. The ^1H NMR signals of the C-4 protons at δ 3.95 and 4.25 may be used to distinguish between **7** and **8** respectively, unless small quantities (<10%) of one epimer are present in the mixture. At that point a more sensitive technique is necessary for accurate assay.

In order to accurately quantitate the presence of even a small amount of **8** within **7**, an analytical HPLC assay of the epimers was devised by the use of an efficient μPorosil (silica) column and an isocratic mobile phase of heptane–CH_2Cl_2–2-propanol (56:40:4). Under these conditions base line analytical separation of the epimers was obtained, although the same conditions were not preparatively useful due to the lower efficiency of the preparative cartridge. Using this technique, we confirmed that **7**, as isolated by preparative HPLC, was indeed contaminated by **8**. From the behavior of the epimeric mixture on the preparative silica cartridge, there is some evidence that epimerization of **7** and **8** occurred on the column itself. For each preparative run, a greater amount of **8** was recovered from the column after several recycles than was calculated to be in the original product mixture on the basis of ^1H

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NMR integration. Further, 7 and 8 are known to be acid labile,[14] and silica gel has been shown to catalyze acid-sensitive reactions.[17] On this basis it seemed that the hydroxy ketones were unlikely candidates for facile chromatographic separation and isolation. Accordingly, we turned to the corresponding ethylene ketals 11 and 12.

A mixture of 7 and 8 was converted to a mixture of 11 and 12 by using ethylene glycol, C_6H_6, and *p*-toluenesulfonic acid (Scheme III). Unlike the hydroxy ketones, 11 and 12 were eminently separable by flash column chromatography on basic alumina using CH_2Cl_2 as the eluent. Moreover, the formation of the ketal appears to be under thermodynamic control, and a new equilibrium ratio of 11:12 was approached if the reaction was allowed to proceed beyond the time needed for initial ketal formation. Presumably due to the increased intramolecular steric interaction present in 12, 11 became the favored epimer in the mixture to the extent of about 55%. Structure elucidation of each of the epimeric hydroxy ketals was accomplished spectrometrically and by reconversion to the respective hydroxy ketone (vide infra). Examination of the ^{13}C NMR spectra of the two products revealed that the C-4 absorption for the now major (equatorial) product 11 was at 5.0 ppm higher field than the corresponding one for the minor (axial) product 12. This fact is consistent with the observed resonances in all of the other 2,4-disubstituted adamantanes studied to date: a carbon bearing a 4(e)-substituent resonates at 3–7 ppm higher field than a carbon bearing a 4(a)-substituent. This condition holds regardless of the identity of the 2-substituent,[15,18-21] although the reason for this consistent chemical shift is not presently clear. Also, the minor product (12) exhibited absorptions in the infrared region in dilute $CHCl_3$ solution consistent with intramolecular H-bonding, with O–H stretching peaks at 3611 and 3480 cm^{-1}, while the major product (11) exhibited only free O–H stretching absorptions in dilute solution.

To regenerate 7 and 8 from 11 and 12, respectively, it was necessary to avoid conditions under which epimerization could take place. We found that by stirring 12 with a trace of *p*-toluenesulfonic acid in 70% aqueous acetone at 25 °C for 12 h, 8 was produced in nearly quantitative yield exclusive of 7. A similar hydrolysis process occurred for 11, except that the solution had to be warmed to 35–40 °C and two treatments were necessary to completely effect conversion. The product recovered from the hydrolysis of 11 under these conditions showed one peak on HPLC analysis that was identical with the minor peak of the original mixture of 7 and 8. Moreover, the ^{13}C NMR spectrum showed ten peaks that were superimposable with the ten minor peaks of the ^{13}C NMR spectrum of the original mixture of 7 and 8. Significantly, none of 8 was detectable in the hydrolysis product of 11. Similarly, HPLC and ^{13}C NMR analysis of the hydrolysis product mixture from 12 was consistent with the presence of only 8. This approach thus represents a substantially improved synthesis of both the 4(a)- and especially the 4(e)-hydroxy-2-adamantanones, which have been until now difficult to obtain.

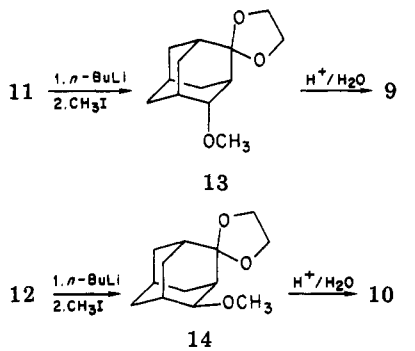
To determine the acid-catalyzed epimerization liability for 7 and 8 during hydrolysis, each was subjected to more vigorous hydrolytic and epimerization conditions than above. The resulting products were then analyzed by HPLC. The results are shown in Table I. From these data and the above results it is clear that 7 is more acid labile than 8, but the epimerization rates of both are sufficiently slow at temperatures below 40 °C that hydrolysis occurs without rearrangement. However, conditions favorable to the attainment of thermodynamic equilibrium do exist. When either 7 or 8 was subjected to the conditions used for ketal formation, but in the absence of ethylene glycol, attainment of the previously observed 25:75 equilibrium mixture of 7:8 was observed (Table I). Similarly, if either pure 11 or pure 12 was subjected to identical conditions with the inclusion of ethylene glycol, the above equilibrium mixture of 55:45 was also reached, although the rate of attainment of this equilibrium was quite slow, especially in the case of 12.

Table I. Epimerization of 7 and 8 under Acidic Aqueous Conditions

compd	solvent	T, °C	time, h	ratio 7:8
8	*a*	56	24	<1:>99
	a	100	2	3:97
	a	100	96	21:79[c]
	b	80	48	25:75[c]
7	*a*	56	24	11:89
	a	100	2	3:97
	a	100	96	21:79[c]
	b	80	24	25:75[c]

[a] 70% aqueous acetone plus traces of *p*-toluenesulfonic acid. [b] Benzene plus traces of *p*-toluenesulfonic acid. [c] No further change observed after heating for longer times.

Scheme IV



In light of the lability of 7 under basic conditions,[16] the syntheses of the corresponding 4(e)- and 4(a)-methoxy derivatives of this system (13 and 14) was undertaken using ketals 11 and 12 (Scheme IV). Thus, treatment of both 11 and 12 with *n*-BuLi in THF followed by CH_3I afforded the corresponding methoxyketals 13 and 14, and spectral analysis (^{13}C NMR) of each of the products confirmed that epimerization did not occur during the alkylation of either isomer. We subsequently found that removal of the ketal function from each product was easily accomplished under the above mild aqueous acidic conditions to product the corresponding methoxyketones 9 and 10. Again, ^{13}C NMR and HPLC analysis (μPorosil, 95:5 heptane:2-propanol) confirmed that no epimerization occurred during hydrolysis. On the basis of these results, we can now report a high yield synthesis of each of the epimeric products 9 and 10 free of the other.

To determine the acid labilities of 9 and 10, we subjected each of the products to conditions identical with those used to study the epimeric hydroxyketones 7 and 8. Interestingly, no epimerization was observed under any of the

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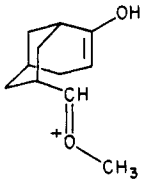
experimental conditions. It thus appears that formation of a suitably protected function at the 4-position will maintain the configurational integrity of either epimer during further synthetic manipulation of the adamantane nucleus. The decreased epimerization liability of **9** relative to **7** may be due to its decreased ability to support the acid-catalyzed π-route fragmentation process postulated by Faulkner and McKervey.[10] The formation of an intermediate alkylated oxonium ion such as **15** may be either



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disfavored or unable to support the rearrangement process, thus stabilizing the configuration at C-4 in this system.

Experimental Section

Melting points were taken on a Thomas-Hoover Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained on either a Beckman 620MX or a Beckman Acculab-3 spectrophotometer. ^{1}H NMR spectra were taken on a Perkin-Elmer R24B instrument, and chemical shifts are reported relative to tetramethylsilane. ^{13}C NMR spectra were obtained on either a Bruker WP-60 or a Varian CFT-20 spectrometer relative to tetramethylsilane as internal standard. Chromatographic analyses were performed with a Waters HPLC system (M6000A pump, U6K injector, and Model 440 UV detector fixed at λ 280 nm). Peak integrations were performed automatically by using a Waters Data Module.

A mixture of 4(e)- and 4(a)-hydroxyadamantan-2-ones (**7** and **8**) was prepared by using the method of Numan and Wynberg[6] starting frm *endo*-bicyclo[3.3.1]non-6-ene-3-carboxylic acid (**3**).

Spiro[4(e)- and 4(a)-hydroxadamantane-2,2′-[1,3]dioxolane] (11 and 12). A mixture of 16.469 g (0.0992 mol) of a mixture of **7** and **8** (21.7% **7**, 78.3% **8**), 34.0 mL (0.609 mol) of ethylene glycol, and 10 mg of *p*-toluenesulfonic acid monohydrate in 400 mL of dry C_6H_6 was heated to reflux for 2 days. The water formed in the reaction was collected in a Dean-Stark trap. The reaction mixture was cooled, diluted with 300 mL of Et_2O, washed with 5% $NaHCO_3$ (2 × 50 mL) and water (2 × 50 mL), and then dried over Na_2SO_4 and evaporated to produce 19.6 g (94%) of a viscous oil. The two epimeric products **11** and **12** were separated on a column containing 750 g of basic Al_2O_3 (activity grade II), using CH_2Cl_2 as the eluent. The axial epimer (**12**) eluted first as 15.4 g (78%) of a colorless oil: bp 113–116 °C (0.5 mm); IR (neat) 3518, 1417, 1127, 1081, 1031 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.4–2.45 (12 H, m), 3.6–4.3 (2 H, m, CHOH), 3.92 (4 H, s, OCH_2); ^{13}C NMR ($CDCl_3$) δ 25.7 (C7), 29.1 (C9), 34.2 (C10), 34.5 (C5), 36.3 (C1 and C6), 41.4 (C3), 63.8 (C12), 64.5 (C11), 76.3 (C4), 111.9 (C2); mass spectrum, M$^+$ calcd for $C_{12}H_{18}O_3$, *m/e* 210.1256; found, *m/e* 210.1255.

Further elution with CH_2Cl_2 produced 4.2 g (22%) of **11** as fine white crystals: mp 63.5–65 °C; IR (nujol) 3457, 1127, 1091, 1050, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2–2.3 (12 H, m), 3.88 (4 H, s, OCH_2), 3.70–4.15 (1 H, m, C*H*OH), OH not assignable; ^{13}C NMR ($CDCl_3$) δ 26.4 (C7), 28.2 (C10), 30.5 (C6), 32.0 (C5), 33.4 (C9), 34.5 (C8), 35.6 (C1), 43.1 (C3), 64.0 (C12), 64.2 (C11), 71.3 (C4), 111.6 (C2); mass spectrum, M$^+$ calcd for $C_{12}H_{18}O_3$; *m/e* 210.1256; found, *m/e* 210.1257.

4(e)-Hydroxyadamantan-2-one (7). A solution of 100 mg (0.476 mmol) of **11** and ca. 10 mg of *p*-toluenesulfonic acid monohydrate in 10 mL of 70% aqueous acetone was stirred at 35 °C for 12 h. The solution was reduced in volume under a stream of N_2. To the product was added 25 mL of CH_2Cl_2. The organic phase was washed with 5% $NaHCO_3$ (2 × 30 mL) and water (30 mL), then dried over $MgSO_4$, and evaporated to yield 79 mg (100%) of **7** after recrystallization from THF–petroleum ether: mp >300 °C. All spectral data were identical with those previously reported.[10]

4(a)-Hydroxyadamantan-2-one (8). A solution of 100 mg (0.476 mmol) of **12** and approximately 10 mg of *p*-toluenesulfonic acid monohydrate in 10 mL of 70% aqueous acetone was stirred at room temperature for 12 h. This was worked up in a manner identical with **7** to yield 79 mg (100%) of **8** after recrystallization from THF–petroleum ether: mp >300 °C. All spectral data were identical with published values.[10]

Spiro[4(e)-methoxyadamantane-2,2′-[1,3]dioxolane] (13). To a stirred solution of 1.780 g (8.50 mmol) of **11** in dry THF was added 7 mL of 1.55 M *n*-BuLi (10.5 mmol) under N_2. After 1 h of stirring, 10 mL (0.16 mol) of CH_3I was added. The mixture was further stirred for 24 h and then poured into ice water. The aqueous phase was saturated with NaCl and extracted with Et_2O (3 × 30 mL). The combined extracts were washed with 5% $NaHCO_3$ (2 × 50 mL) and H_2O (50 mL), then dried over Na_2SO_4, and evaporated to product 1.898 g (99.7%) of a yellow oil. The oil was placed on a column of basic Al_2O_3 (activity grade II) and eluted with CH_2Cl_2 to yield 1.191 g (62.5%) of **13** as a colorless oil: bp 104–105 °C (0.7 mm); IR (neat) 2934, 2912, 1465, 1450, 1383, 1366, 1125, 1103, 1088, 948 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.1–2.2 (12 H, m), 3.35 (3 H, s, OCH_3), 3.35–3.6 (1 H, br s, C*H*OCH_3), 3.9 (4 H, s, OCH_2); ^{13}C NMR ($CDCl_3$) δ 26.3 (C7), 28.7 (C10), 30.1 (C5), 30.8 (C6), 31.8 (C5), 34.6 (C6), 35.9 (C1), 40.4 (C3), 55.6 (C13), 64.1 (C12), 64.3 (C11), 80.5 (C4), 111.4 (C2); mass spectrum, M$^+$ calcd for $C_{13}H_{20}O_3$, *m/e* 224.1413; found, *m/e* 224.1413. Remaining starting material (**11**) was recovered with a CH_2Cl_2 wash of the column.

Spiro[4(a)-methoxyadamantane-2,2′-[1,3]dioxolane] (14). To a stirred solution of 3.861 g (18.4 mmol) of **12** in dry THF was added 15.0 mL of 1.55 M *n*-BuLi (23.3 mmol) under N_2. After 1 h of stirring, 20 mL (0.32 mol) of CH_3I was added. The solution was stirred for 24 h and then worked up in a manner identical with that for **13** to produce 3.991 g (69.8%) of **14** as a yellow oil: bp 105–107 °C (0.3 mm); IR (neat) 2915, 2864, 1464, 1449, 1390, 1379, 1131, 1110, 1091, 914 cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.4 (12 H, m), 3.3–3.8 (4 H, m, $CHOCH_3$), 3.8–4.2 (4 H, m, OCH_2); ^{13}C NMR ($CDCl_3$) δ 26.3 (C7), 29.4 (C9), 31.0 (C5), 34.5 (C10), 34.6 (C8), 35.6 (C1), 36.7 (C6), 39.2 (C3), 56.2 (C13), 63.1 (C12), 64.8 (C11), 85.6 (C4), 110.8 (C2); mass spectrum, M$^+$ calcd for $C_{13}H_{20}O_3$, *m/e* 224.1413; found, *m/e* 224.1415.

4(e)-Methoxyadamantan-2-one (9). A solution of 130.8 mg (0.584 mmol) of **13** and approximately 10 mg of *p*-toluenesulfonic acid monohydrate in 10 mL of 70% aqueous acetone was stirred at 45 °C for 48 h. The product was worked up in the same manner as **7** to yield 111.8 mg (94%) of **9** as an oil: bp 89–92 °C (0.5 mm); IR (neat) 2934, 1715, 1465, 1450, 1383, 1125, 1088 cm^{-1}; NMR ($CDCl_3$) δ 1.2–3.1 (12 H, m), 3.3–3.6 (4 H, m, $CHOCH_3$); ^{13}C NMR ($CDCl_3$) δ 26.8 (C7), 30.18 (C6), 31.1 (C5), 33.0 (C10), 33.2 (C9), 38.9 (C8), 45.7 (C1), 50.8 (C3), 55.9 (C11), 81.8 (C4), 214.9 (C2); mass spectrum, M$^+$ calcd for $C_{11}H_{16}O_2$, *m/e* 180.1151; found, *m/e* 180.1148.

4(a)-Methoxyadamantan-2-one (10). A solution of 205 mg (0.916 mmol) of **14** and approximately 10 mg of *p*-toluenesulfonic acid monohydrate in 10 mL of 70% aqueous acetone was stirred at room temperature for 12 h. The product was worked up in a manner identical with **7** to afford 164 mg (99%) of **10** as a colorless oil: bp 102–104 °C (0.3 mm); IR (neat) 2933, 2864, 1765, 1451, 1180, 1106, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2–3.1 (12 H, m), 3.2–3.4 (3 H, s, OCH_3), 3.6–3.8 (1 H, s, C*H*OCH_3). ^{13}C NMR ($CDCl_3$) δ 26.8 (C7), 31.1 (C5), 33.2 (C9), 35.2 (C6), 37.8 (C10), 39.0 (C8), 46.4 (C1), 51.0 (C3), 55.5 (C11), 86.5 (C4), 215.9 (C2); mass spectrum, M$^+$ calcd for $C_{11}H_{16}O_2$, *m/e* 180.1151; found, *m/e* 180.1151.

HPLC assays for **7** and **8** were performed with a Waters μPorosil column (3.9 mm × 30 cm) using heptane–CH_2Cl_2–propanol (56:40:4) as the mobile phase at a flow rate of 0.7 mL/min. The respective capacity factors (*k's*) were 2.27 and 2.09. Quantitation of **7** and **8** was accomplished by using a Beer's law plot to obtain ϵ of 19.5 and 21 respectively. The HPLC assays for **9** and **10** were run by using an identical column and a heptane–2-propanol (95:5) mobile phase at 2.0 mL/min flow. Capacity factors were 1.48 and 1.88 and epsilons were 55.8 and 25, respectively.

Equilibrium Studies. A. Aqueous Acetone. A sample (approximately 100 mg) of the compound and approximately 10 mg of *p*-toluenesulfonic acid monohydrate in 5 mL of 70%

aqueous acetone was sealed in a Carius combustion tube and heated to the specified temperature for the desired amount of time. The tube was then cooled, the acetone removed with a stream of N_2, and the resulting solution taken up in 25 mL of CH_2Cl_2. This was washed with 5% $NaHCO_3$ (2 × 30 mL) and water (30 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting products were then subjected to HPLC analysis.

B. Benzene Solution. A mixture of ca. 100 mg of the compound and 10 mg of *p*-toluenesulfonic acid monohydrate in 25 mL of dry C_6H_6 was heated to reflux for 2 days. The reaction mixture was cooled and diluted with 20 mL of Et_2O, washed with 5% $NaHCO_3$ (2 × 20 mL) and water (20 mL), dried over Na_2SO_4, and evaporated to dryness. The resulting product was then subjected to HPLC analysis.

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Quinolizidine Alkaloid Synthesis via the Intramolecular Imino Diels–Alder Reaction. *epi*-Lupinine and Cryptopleurine

Martin L. Bremmer, Nazir A. Khatri, and Steven M. Weinreb*

Department of Chemistry, The Pennsylvania State University, University Park, Pennsylvania 16802

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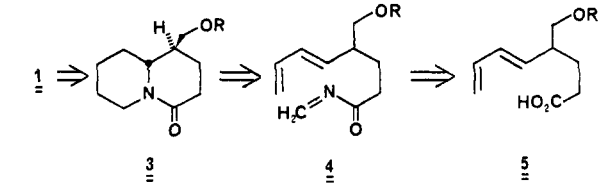
A totally stereoselective total synthesis of *epi*-lupinine (1) has been developed that starts with methyl sorbate (6). Alkylation of **6** with bromide **8** gave diene **10**, which was elaborated into the imino Diels–Alder precursor **17**. Thermolysis of **17** provided exclusively bicyclic lactam **18**. Acyl imine **4** (R = CH_2Ph) has been postulated as an intermediate in this cycloaddition. The stereoselectivity of the reaction is rationalized on the basis of a transition state, **22**, which has (1) a planar, *s*-cis acyl imine moiety, (2) a carbonyl group endo to the diene, and (3) a quasi-boat bridging-chain conformation. Reduction of **18** afforded racemic *epi*-lupinine. Cryptopleurine (**2**) was prepared by starting from the readily available phenanthrene aldehyde **33**. Cyclization of methylol acetate **37** gave lactam **38**. It was demonstrated that only the *E* form of **37** cyclizes via (*E*)-acyl imine **39**. The *Z* isomer **40** did not lead to a Diels–Alder product. Hydride reduction of lactam **38** gave racemic cryptopleurine.

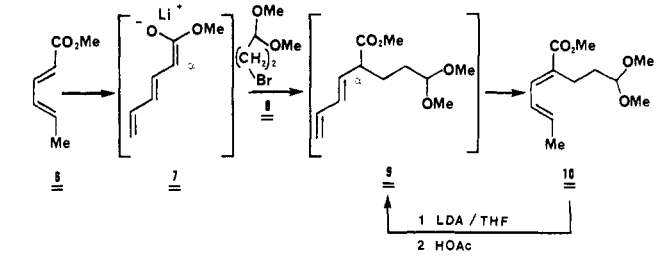
Recent papers from these laboratories have shown the utility of intramolecular Diels–Alder cycloadditions of *N*-acyl imino dienophiles in construction of annulated tetrahydropyridines.[1-3] Previous work has dealt primarily with applications of this methodology to synthesis of several types of indolizidine alkaloids. To date, we have reported total syntheses of δ-coniceine,[1a,d] tylophorine,[1a,d] elaeokanine A and B[1b,d] and slaframine.[1f] In addition, studies have been carried out to probe various stereochemical facets of the process, particularly regarding the relationship of imine substitution and geometry to product relative configuration. One other stereochemical feature investigated in a few cyclizations which formed 6/5 fused rings was the configurational outcome of substituents in the chain-bridging diene and dienophile.[1b,f] In general, Diels–Alder reactions which gave 6/5 systems showed excellent stereoselectivity when carboxyl-substituted *N*-acyl imines[1b,e,4] were used but little stereocontrol with respect to bridge substituents.

As an extension of this work, we wished to determine whether intramolecular imino Diels–Alder chemistry could also be used in synthesis of quinolizidines and to further explore stereochemical features of the reaction in such systems. Toward these ends, we set out to design total syntheses of the quinolizidine alkaloids *epi*-lupinine (**1**)[5] and cryptopleurine (**2**).[6]

Scheme I



Scheme II



In the case of **1**, it was our hope to use an intramolecular imino Diels–Alder strategy to simultaneously generate the quinolizidine ring system and establish the alkaloid relative

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