(1 H, dd, J = 8.3, 2.5 Hz), 4.96 (1 H, dd, J = 9, 2.9 Hz), 4.83 (1 H, ddd, J = 6.9, 3.85, 3.5 Hz), 4.50 (1 H, dd, J = 12.3, 2.5 Hz), 4.42 (q, J = 6.8 Hz), 4.05 (1 H, dq, J = 6.4, 3.5 Hz), 3.99 (1 H, dd, J = 12.3, 8.3 Hz), 3.7 (1 H, dd, J = 12.5, 1.95 Hz), 2.99 (1 H, br s), 2.12, 2.03, 2.0, and 1.98 (4-$COCH_3$), 1.71-1.5 (4 H, m), 1.16 (3 H, d, J = 6.4 Hz), 0.94 (3 H, d, J = 5.6 Hz), 0.85 (3 H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 133.6, 129.8, 98.8, 81.2, 79.4, 77.7, 77.6, 77.5, 73.6, 62.3, 40.2, 40.0, 34.3, 34.1, 27.7, 25.4, 20.9, 18.8, 16.2, 14.9.

Periodate-Permanganate Oxidation of 2. The oxidation stock solution used was freshly prepared by dissolving 448 mg of potassium periodate and 8 mg of potassium permanganate in 100 mL of distilled water with slight warming. A mixture of 30 mg of **2**, 20 mL of *tert*-butyl alcohol, and 50 mL of the oxidation stock solution was brought to pH 8.6 by addition of potassium carbonate and then stirred on a magnetic stirrer for 20 h. The mixture was acidified with 10% sulfuric acid and treated with sodium metabisulfite to convert all the periodate, iodate, and iodine into iodide. The solution was made alkaline with 5% potassium hydroxide, the butanol was distilled off, and the remaining solution was again acidified to pH 3 and continuously extracted overnight with ether. The ether extract was dried over anhydrous magnesium sulfate and then evaporated to dryness to give 16 mg of a mixture of acids. The mixture of acids was converted to the potassium salts and refluxed with 30 mg of *p*-bromophenacyl bromide and 5 mg of 18-crown-6 in 8 mL of acetonitrile for 1 h. The acetonitrile was distilled off, and the residue was purified by preparative layer chromatography (silica gel, $CHCl_3$/MeOH 95:5). Among several other degradation products, 5.7 mg of the bromophenacyl ester of the compound **3** derived from the tetrahydropyran moiety of aplasmomycin was isolated. Its structure follows from the ^1H NMR, ^{13}C NMR, and mass spectra. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (2 H, d, J = 8.6 Hz), 7.61 (2 H, d, J = 8.6 Hz), 5.27 (2 H, AB q), 4.5 (1 H, dd, J = 4.4, 6.9 Hz), 3.74 (1 H, dd, J = 1.6, 4.9 Hz), 2.84 (1 H, dd, J = 4.9, 18.7 Hz), 2.7 (1 H, m), 2.57 (1 H, dd, J = 2.5, 18.7 Hz), 2.10 (1 H, m), 1.68 (2 H, m), 1.25 (3 H, d, J = 7 Hz), 1.05 (3 H, s), 0.94 (3 H, s); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 191.3, 175.6, 170.0, 133.0, 132.2, 129.9, 129.1, 81.9, 72.9, 65.6, 38.6, 36.7, 36.5, 30.0, 26.5, 21.9, 18.9, 17.2; MS (CI), $(M + H)^+$ 441.085, 443.081, calcd 441.091, 443.089.

Acknowledgment. We are indebted to the University of Illinois NMR Resource (supported by NSF) for deuterium NMR spectra, to Kyungook Lee for the chirality analyses of acetate samples, and to the National Institutes of Health for financial support through Research Grant AI 20264.

Registry No. 1, 61230-25-9; **2**, 109432-24-8; **3**, 109391-17-5; glycerol, 56-81-5.

Intramolecular Cyclopropanation of Enol Ethers: Synthetic Approach to Medium-Sized Carbocycles†

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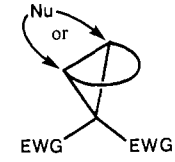
Abstract: The transannular cyclopropanation reactions of ketocarbenes, generated by $[Rh(OAc)_2]_2$ catalysis, on the 2-substituted 3,4-dihydropyran nucleus was explored. The scope and limitations of the cyclopropanation reaction were defined and where successful, and the reaction produced novel oxa-tricyclic ketones. In cases where the cyclopropanation failed, interesting and novel intramolecular C-H insertions occurred, and these could be rationalized on the basis of chain length of the diazo ketone, and substitution on the dihydropyran ring. The oxa-tricyclic ketones were subjected to acidic media and the presence of the appropriate nucleophiles and reaction conditions led to cyclopropane ring fragmentation and the formation of new carbocycles. By using this methodology, a practical approach to 6-9-membered carbocycles is described, whereby the stereochemistry of the annular substituents is controlled.

Fused and bridged polycyclic systems containing a cyclopropane ring have been shown to be useful intermediates in organic synthesis.[1] The torsional strain in the 3-membered ring imparts a high degree of reactivity, which can lead to the fragmentation of the cyclopropane. This process is hopefully a regio- and stereochemically controlled one.

One such example makes use of the homoconjugate addition of a nucleophile to a cyclopropane activated by electron-withdrawing groups (EWG). There are two important considerations associated with this approach: (a) for ring cleavage with carbon nucleophiles, the cyclopropane usually must be doubly activated by two electron-withdrawing substituents (i.e., two carbonyl functions), otherwise homoconjugate addition does not occur,[2,3] and (b) there may or may not be regiochemical discrimination in the opening of the cyclopropyl ring (Scheme I).[4]

Scheme I. Homoconjugate Addition on Activated Cyclopropanes



This paper describes the synthesis of oxa-tricyclic cyclopropyl ketones whereby both of these points are taken into consideration

† This paper is dedicated to Professor Gilbert Stork on the occasion of his 65th birthday.

‡ Merck Frosst Canada Inc.

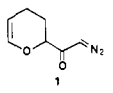
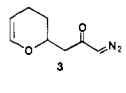
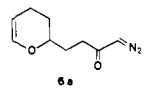
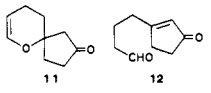
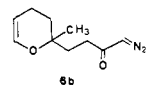
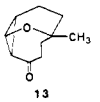
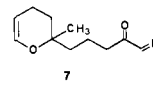
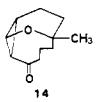
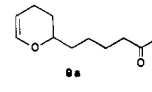
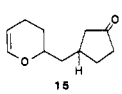
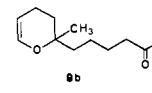
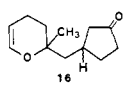
§ Merck Sharp & Dohme Research Laboratories.

(1) (a) Dave, V.; Warnhoff, E. W. *Organic Reactions*; John Wiley & Sons, Inc.; New York, 1970; Vol. 18, Chapter 3, pp 217-401. (b) Burke, S. D.; Grieco, P. A. *Organic Reactions*; John Wiley & Sons, Inc.; New York, 1979; Vol. 26, Chapter 2, pp 361-475 and references therein.

(2) (a) Trost, B. M.; Taber, D. F.; Alper, J. B. *Tetrahedron Lett.* **1976**, *17*, 3857. (b) House, H. O.; Weeks, P. D. *J. Am. Chem. Soc.* **1975**, *97*, 2778. (c) Corey, E. J.; Fuchs, P. L. *J. Am. Chem. Soc.* **1972**, *94*, 4014. (d) Daviaud, G.; Miginiac, Ph. *Tetrahedron Lett.* **1972**, *13*, 997.

0002-7863/87/1509-5432$01.50/0

Table I. Intramolecular Carbene Cyclopropanations and Insertions

	SUBSTRATE	PRODUCT(S)	YIELD (%)	I.R. C=O STRETCH (cm^{-1})
1)	 1	 2	58[b]	1740
2)	 3	 10	61[c]	1890
3)	 5a	 11 12	>95[d]	—
4)	 6b	 13	>95[d]	1665
5)	 7	 14	80[d]	1675
6)	 9a	 15	91[c]	1740
7)	 9b	 16	84[c]	1740

[a] Only C=O stretching frequencies for oxa-tricyclic ketones are shown. [b] Overal yield from commercially available 3,4-dihydro-2*H*-pyran-2-carboxylic acid, sodium salt. [c] Purified yield from flash chromatography. [d] Crude yield estimated by ^1H NMR.

in the opening of the 3-membered ring by using an acid-catalyzed ring opening of the cyclopropane.[5]

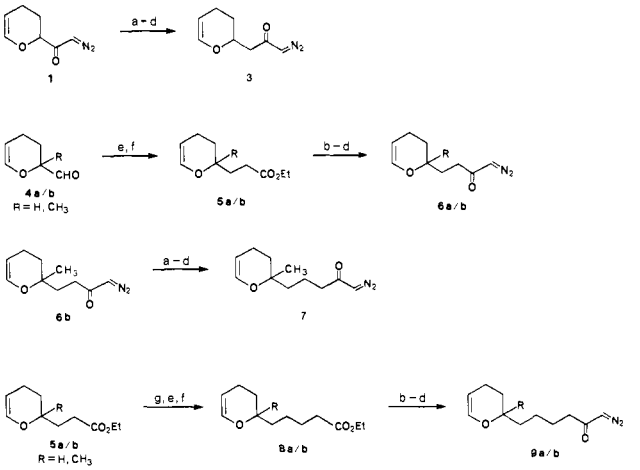
Results and Discussion

We recently described the intramolecular cyclopropanation of an enol ether mediated by a $[Rh(OAc)_2]_2$ catalyzed decomposition of an α-diazo ketone (entry 1, Table I).[6,7] The resultant product, a highly strained oxa-tricyclic ketone **2**, proved to be especially reactive in acidic media, as characterized by the solvolytic addition of nucleophiles to produce oxa-bicyclic ketones.

The high yields and specificity of this reaction prompted us to examine diazo ketones of different chain lengths in an effort to discover the limiting features and synthetic scope of the cyclopropanation reaction. In addition it was felt that the possibility of synthesizing carbocyclic rings (6-membered) existed by effecting a fragmentation of the labile cyclopropane bond.

The preparation of the α-diazo ketones was a straightforward matter. In the case of the one-carbon homologue of **1** the

Scheme II. Preparation of Diazo Ketones



[a] AgOBz, Et_3N/MeOH, 50 °C. [b] 1 N NaOH/MeOH. [c] $(COCl)_2$, cat. DMF/CH_2Cl_2. [d] CH_2N_2/Et_2O, 0 °C. [e] $Ph_3P{=}CHCO_2Et$/PhMe, 60 °C. [f] Cu_2Br_2, Vitride, THF, *t*-BuOH or Et_3SiH neat/cat. $[Ph_3P]_3RhCl$, 100 °sC. [g] DIBAL-H/PhMe, −78 °C.

Arndt–Eistert reaction[8] in MeOH was employed to produce the chain-extended methyl ester which was saponified and converted to the diazo ketone **3** with standard conditions. The two-carbon homologue of **1** was prepared by starting with the dihydropyran carboxaldehyde **4a/b** (R = H, Me). A Wittig reaction with (carboethoxymethylene)triphenylphosphorane provided the α,β-unsaturated esters in excellent yield. The double bond was reduced by either of two methods: (1) "CuH", giving quantitative yields,[9] or (2) $Et_3SiH/[Ph_3P]_3RhCl$, affording lower yields but more easily amenable to large scale.[10] The esters **5a/b** were then routinely converted to their corresponding diazo ketones **6a/b**.

The three-carbon homologue of **1** once again made use of the Arndt–Eistert one-carbon extension from diazo ketone **6b** and eventually producing diazo ketone **7**. Finally, synthesis of the 4-carbon homologues of **1** involved a second Wittig reaction on the aldehydes obtained by DIBAL reduction of esters **5a/b**, followed by reduction of the double bond ($Et_3SiH/(Ph_3P)_3RhCl$) to give esters **8a/b**. Conversion to diazo ketones **9a/b** proceeded uneventfully (Scheme II).

Cyclization Experiments

The use of $[Rh(OAc)_2]_2$ as an effective and mild catalyst to generate carbenoid species has been well documented.[11]

Typically the reactions are run at room temperature in dry CH_2Cl_2 employing 1–2 wt % of catalyst, followed by slow addition of the substrate. Progress could be conveniently monitored by TLC, and the cessation of nitrogen evolution signaled the completion of the reaction. The results of the cyclization experiments are summarized in Table I. In entries 1, 2, 4, and 5, oxa-tricyclic ketones were produced in good yield and no other products were observed. However, due to their chemical instabilities, attempts to purify either by distillation or column chromatography resulted in substantial loss in yield due to decomposition.

In most cases the crude tricyclic product was found to be practically pure by ^1H NMR analysis and was simply carried on to the next stage. It is interesting to note that the carbonyl stretching frequencies in the IR spectra are somewhat indicative of the relative stabilities of the tricyclic ketones. For instance the

(3) Special cases of nucleophilic opening of cyclopropanes with non-carbon nucleophiles have been reported, see: (a) Fleming, A.; Sinai-Zingde, G.; Natchus, M.; Hudlicky, T. *Tetrahedron Lett.* **1987**, *28*, 167. (b) Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412. (c) Truce, W. E.; Lindy, L. B. *J. Org. Chem.* **1961**, *26*, 1463. (d) Smith, A. B.; Scarborough, R. B., Jr. *Tetrahedron Lett.* **1978**, *17*, 1649. (e) Schweizer, E. D.; Berninger, C. J.; Thompson, J. G. *J.* Org. *Chem.* **1968**, *33*, 336.

(4) An excellent review of electrophilic cyclopropane ring cleavage appears by Danishefsky, S.; *Acc. Chem. Res.* **1979**, *12*, 66.

(5) Acid-catalyzed ring opening of oxacyclopropane carbonyl compounds has been documented, see: Doyle, M. P.; Van Leusen, D. *J. Org. Chem.* **1982**, *47*, 5326.

(6) Adams, J.; Belley, M. *Tetrahedron Lett.* **1986**, *27*, 2075.

(7) For other examples of cyclopropanation of enol ethers and their ring-opening reactions, see: Wenkert, E. *Acc. Chem. Res.* **1980**, *13*, 27.

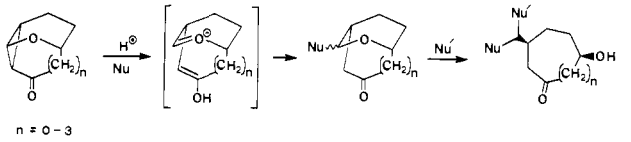
(8) Hudlicky, T.; Sheth, J. P. *Tetrahedron Lett.* **1979**, *20*, 2660.

(9) Semmelhack, M. F.; Stauffer, R. D. *J. Org. Chem.* **1975**, *40*, 3619.

(10) Yoshii, E.; Kobayashi, Y.; Koizumi, T.; Oribe, T. *Chem. Pharm. Bull* **1974**, *22*, 2767.

(11) (a) Doyle, M. P.; Griffin, J. H.; Bugheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53. (b) Doyle, M. P.; Dorow, R. L.; Tamblyn, W. H.; Buhro, W. E. *Tetrahedron Lett.* **1982**, *23*, 2261. (c) Doyle, M. P.; Van Lensen, D.; Tamblyn, W. H. *Synthesis* **1981**, *10*, 787. (d) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petinot, N.; Teyssiê, P. *J. Org. Chem.* **1980**, *45*, 695.

Scheme III. Mechanism of Ring Fragmentation in Acidic Media



π orbital of ketone **2** has the poorest overlap with the cyclopropane and **2** is the most stable to hydrolysis on silica gel. Ketones **13** and **14** are the least stable to silica, and the ketone π orbitals substantially overlap with the cyclopropane as seen by the lower energy stretching frequencies, which are similar to those of enones. This is supported by examination of molecular models. The mechanism for hydrolysis is addressed subsequently.

Entry **3** exhibits an interesting C–H insertion reaction in preference to cyclopropanation. The intermediacy of a six-membered ring ylide presents itself as a possibility, although a conventional C–H insertion mechanism might also be operative. Recently, both Pirrung and Johnson independently described similar ylides.[12,13] Attempts to purify the spirocyclic compound **11** through a silica gel column led to the formation of the aldehyde cyclopentenone **12**, via a β-elimination process.

In entry 4 the diazo ketone **6b** bears an angular methyl group and still has the possibility of forming an oxygen ylide; however, the insertion reaction α to oxygen cannot occur, and cyclopropanation proceeds smoothly.

Entries 6 and 7 demonstrate the limiting case for the cyclopropanation reaction. The carbon chains are too long and the carbene exhibits a kinetic preference for insertion into an unactivated C–H bond to form 5-membered rings (1:1 diastereomeric mixture). The assignment of structures **15** and **16** (Table I) was made largely by analysis of the mass spectral fragmentation patterns and by the carbonyl stretching frequency in the infrared spectra. The kinetic preference for the formation of a 5-membered ring in favor of the 6-membered ring has been well documented.[14] It is interesting that the diazo ketone **7**, also capable of forming a cyclopentanone, reacts only to form the cyclopropane. The reactivity difference is that of the electron-rich enol ether vs. the hindered unactivated C–H bond (α to a quarternary center). This result is mechanistically interesting in that the potential intermediate ylide proposed for the case of entry 2, has no bearing on the outcome of these reactions.

Ring Fragmentation

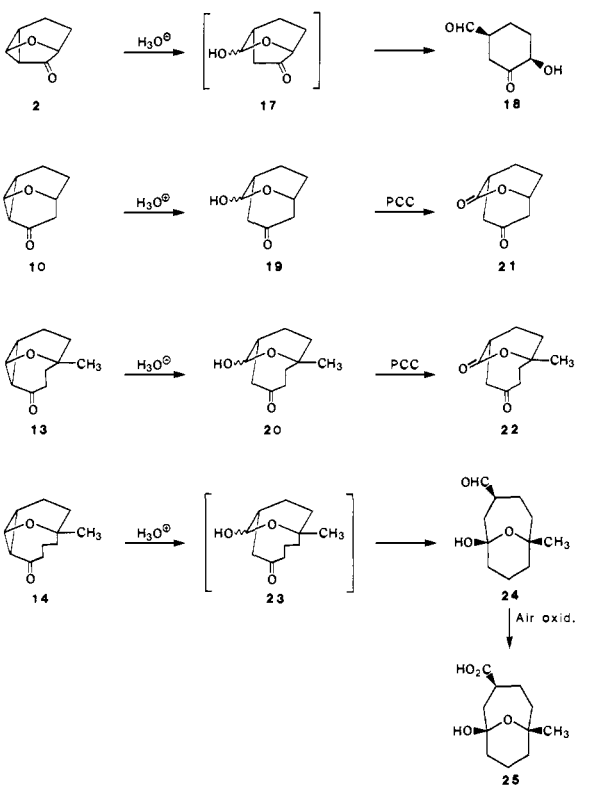
As already mentioned the strained cyclopropane compounds are reactive to acidic conditions and nucleophiles can add in homoconjugate fashion. In acidic media, the intermediacy of an enol oxonium ion is postulated (Scheme III), which upon addition of a nucleophile (i.e., solvolysis) produces a bicyclic ketone.

Further ring cleavage of the C–O bond would give rise to a ring-expanded carbocyclic ketone bearing two remote annular functions having a syn relationship. Depending on the lengths of the initial diazo ketone chain, various medium-sized rings could be formed. To this purpose, a number of reaction sequences were explored.

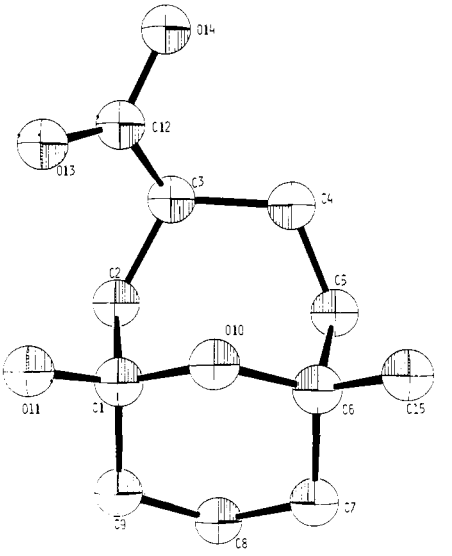
Solvolysis of tricyclic ketone **2** ($TsOH/THF/H_2O$) afforded, in quantitative yield, the 6-membered-ring α-hydroxy ketone **18**, and the intermediate hemiacetal **17** was not observed. Alternatively, under the same conditions the compounds **10** and **13** afforded exclusively the hemiacetals **19** and **20** respectively. The seven- and eight-membered carbocycles were not observed.

The stable hemiacetals **19** and **20** were oxidized (PCC, NaOAc) to give the corresponding lactones **21** and **22** in good yield, which are viewed as functional precursors to the 7- and 8-membered-ring cyclic ketones. Hydrolysis of the tricyclic ketone **14** initially formed the keto-lactol (not observed) and equilibrated to a new

Scheme IV. Hydrolysis of Oxa-Tricyclic Ketones



Scheme V. X-ray Crystal Structure Analysis of Acid **25**



lactol-aldehyde **24** which may be regarded as a 9-membered-ring precursor (after saponification). The aldehyde **18** is initially diastereomerically pure but epimerizes during chromatography on silica gel.[15]

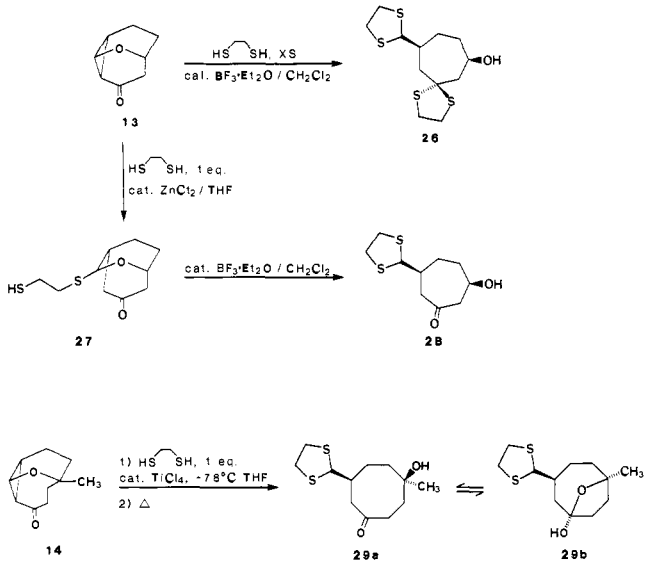
However, when the aldehyde **24** was left standing in air in a $CHCl_3$ solution, it slowly oxidized to the corresponding carboxylic acid **25**, which crystallized.[15] The stereochemistry of the carboxyl group was confirmed by X-ray crystallography (Scheme V).

Another synthetic sequence involved treating the tricyclic ketone **13** with excess ethanedithiol in the presence of $BF_3 \cdot Et_2O$ to obtain the 7-membered-ring bis(dithioketal) **26**. Differention of the two carbonyls was possible with a 2-step sequence: (1) ethanedithiol (1.0 equiv) cat. $ZnCl_2/THF$, (2) $BF_3 \cdot Et_2O/CH_2Cl_2$. In this

(12) Pirrung, M. C.; Werner, J. A. *J. Am. Chem. Soc.* **1986**, *108*, 6060.
(13) Roskamp, E. J.; Johnson, C. R. *J. Am. Chem. Soc.* **1986**, *108*, 6062.
(14) Preference for 5-membered-ring formation has been demonstrated by: (a) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. (b) Wenkert, E.; Davis, L. L.; Mylan, B. L.; Solomon, M. F.; da Silva, R. F.; Warnet, R. J. *J. Org. Chem.* **1982**, 3242.

(15) Both the ease of epimerization and oxidation of the aldehyde moiety appear to be activated substantially by the proximity of the angular hydroxyl group, which is within hydrogen bonding distance of the carbonyl oxygen (cf. X-ray structure Scheme V).

Scheme VI. Carbonyl Differentiation and Ring Expansion

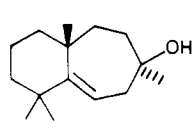


manner only the aldehyde function is masked. In the case of ketone **14** the same reaction is achieved in one pot beginning with cat. $TiCl_4$/THF/−78 °C, then ethanedithiol followed by heating to reflux to produce the 8-membered ring ketone **28a** which is in equilibrium with the corresponding hemiacetal **28b**.

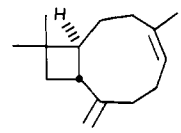
The synthesis of medium-sized rings poses a challenge to the organic chemist. In addition, the control of stereochemical elements in larger rings requires a much more sophisticated understanding of the conformation options. The sequences described for the syntheses of 6–9-membered rings make use of conformationally restricted oxa-tricyclic systems, which when unravelled produce functionality remotely placed on the newly formed carbocycle with a predictable relative stereochemical outcome.

The oxygen functionality on the ring-expanded carbocycles may be differentiated either by manipulation of their oxidation states or by selective protection during ring fragmentation.

The examples described are the simplest test cases. We are currently exploring more complex dihydropyrans (glycals) with various functionality adorning the original heterocycle. Particular attention is being paid relevant functionality toward the synthesis of sesquiterpenoids containing 6,7 fused rings and 4,9 fused rings examplified by natural products widdrol and isocaryophyllene, respectively.



widdrol



isocaryophyllene

Experimental Section

Preparation of Diazo Ketone 3. (i) **Methyl 3,4-Dihydro-2*H*-pyranyl-2-acetate.** A solution of diazo ketone **1** (20 g, 133 mmol) in dry MeOH (400 mL) was heated to 40 °C and to this solution was added portionwise (1 mL) with a dropping funnel a solution of silver benzoate (5.0 g, 22 mmol) in triethylamine (45 mL). Evolution of nitrogen was observed as the mixture was heated to 50 °C to initiate the reaction. The mixture was kept at 45 °C and 1-mL portions were added until no further evolution of nitrogen was noticed. The reaction mixture was concentrated under vacuum, and the methyl ester was purified by flash chromatography on silica gel, eluting with 10% EtOAc/hexane to yield the title product (16.5 g, 80%). The methyl ester could also be purified by distillation: bp 79 °C (2 mm Hg). IR 1740, 1650, 1240, 1200, 1065 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.5–2.2 (4 H, complex m), 2.6 (2 H, t, J = 6 Hz), 3.7 (3 H, s), 4.1–4.4 (1 H, m), 4.6–4.8 (1 H, m), 6.35 (1 H, d, J = 6 Hz).

(ii) **Diazo Ketone 3.** To a solution of methyl ester (970 mg, 6.2 mmol) in MeOH (12 mL) was added 1 N NaOH (6.2 mL, 6.2 mmol), and the solution was stirred at room temperature for 2 h. The reaction mixture was evaporated to dryness under vacuum and coevaporated with MeOH (3 × 50 mL) until a white solid was obtained. The solid was dried under high vacuum at 90 °C for 18 h to afford the sodium salt.

A suspension of sodium salt in dry CH_2Cl_2 (30 mL) was cooled to 0 °C and DMF (1 drop) was added. To this mixture was added oxalyl chloride (0.64 mL, 7.4 mmol) dropwise, and the mixture was stirred at this temperature for 30 min.

The resulting solution was transferred to an addition funnel and slowly added, at 0 °C, to a solution of 0.5 M diazomethane in ether (60 mL). The temperature was raised to room temperature over 2 h and the reaction mixture concentrated to about 20 mL. The salts were removed by filtration on Celite, and the diazo ketone was flash chromatographed on silica gel, eluting with 10% EtOAc/hexane to yield the diazo ketone **3** (560 mg, 55%): IR 2100, 1640, 1370, 1060 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.5–2.2 (4 H, complex m), 2.55 (2 H, t, J = 6 Hz), 4.1–4.4 (1 H, m), 4.6–4.8 (1 H, m), 5.35 (1 H, s(b)), 6.3 (1 H, d, J = 6 Hz).

Oxa-Tricyclic Ketone 10. Rhodium(II) acetate dimer (34 mg, 0.08 mmol, 2% by weight) was suspended in freshly distilled CH_2Cl_2 (400 mL). To this suspension, under N_2 at room temperature, was added slowly (using a dropping funnel or a syringe drive (rate 10 mL/h) a solution of diazo ketone **3** (1.7 g, 10.2 mmol) in CH_2Cl_2 (40 mL). One hour after complete addition, the reaction mixture was quenched with 5% aqueous $NaHCO_3$ and the organic layer separated, dried over Na_2SO_4, and filtered. A few drops of triethylamine were added to the filtrate and evaporated to dryness to afford the crude tricyclic ketone (1.37 g, crude 98%) as an orange oil. ^1H NMR showed purity up to 95%. The oil could be flash chromatographed on silica gel (50 g), rapidly eluting with 40% EtOAc/hexane (containing 2% NEt_3) to afford oxa-tricyclic ketone **10** as a colorless oil (890 mg, 61%): IR 1690, 1235, 1220, 1035, 995, 850, 780 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 0.7–0.9 (2H, m), 1.5–1.65 (4 H, complex m), 1.78 (1 H, d, J = 16 Hz), 2.35 (1 H, dd, J = 16, 6 Hz), 3.65–3.72 (1 H, m), 3.75 (1 H, t, J = 6 Hz); MS exact mass calcd for $C_8H_{11}O_2$ (M^+ + 1) 139.076, found 139.076.

Preparation of Ethyl 3-(3,4-Dihydro-2*H*-pyran-2-yl)propanoate (5a). (i) **Ethyl (*trans* and *cis*)-3-(3,4-dihydro-2*H*-pyran-2-yl)acrylate.** To a solution of 3,4-dihydro-2*H*-pyran-2-carboxaldehyde (**4a**) (11.2 g, 100 mmol) in toluene (100 mL) was added (carboethoxymethylene)triphenylphosphorane (34.8 g, 100 mmol), and the mixture was sitrred at 60 °C for 30 min. The reaction mixture was evaporated to dryness under vacuum and the residue was flash chromatographed on silica gel, eluting with 10% EtOAc/hexane to afford pure trans olefin (12.8 g, 70%) and *cis*-olefin (1.9 g, 10%) as oils. Trans olefin: IR 1720, 1650, 1305, 1240, 1060 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.3 (3 H, t, J = 6 Hz), 1.65–1.75 (1 H, m), 1.95–2.15 (3 H, complex m), 4.2 (2 H, q, J = 6 Hz), 4.48–4.55 (1 H, m), 4.7–4.8 (1 H, m), 6.08 (1 H, dd, J = 16, 2 Hz), 6.4 (1 H, d, J = 6 Hz), 6.95 (1 H, dd, J = 16, 3 Hz). Cis olefin: IR 1720, 1650, 1420, 1190, 1055 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.3 (3 H, t, J = 6 Hz), 1.7–1.85 (1 H, m), 1.9–2.08 (2 H, m), 2.1–2.25 (1 H, m), 4.2 (2 H, q, J = 6 Hz), 4.7–4.8 (1 H, m), 5.4 (1 H, t, J = 9 Hz), 5.82 (1 H, dd, J = 9, 1.5 Hz), 6.3–6.4 (2 H, m).

(ii) **Ester 5a.** To a well-stirred suspension of 99.9% copper(I) bromide (14.4 g, 50 mmol) in dry THF (150 mL) kept at 0 °C under N_2 was added dropwise a solution of 70% Vitride in toluene (22.4 mL, 80 mmol). The mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. *tert*-Butyl alcohol (17 mL) was added, followed by a slow addition of a solution of the α,β-unsaturated ester (1.82 g, 10 mmol) in dry THF (40 mL). The mixture was stirred at −20 °C for 2 h and quenched with H_2O (4 mL) The mixture was poured into saturated aqueous NH_4Cl (500 mL) and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated to dryness to give a liquid that was "bulb-to-bulb" distilled (150 °C (1 mm Hg)) to afford the ester **5a** (1.75 g, 96%): IR 1740, 1650, 1240, 1180, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (3 H, t, J = 6 Hz), 1.5–1.7 (1 H, m), 1.8–1.95 (3 H, complex m), 1.95–2.15 (2 H, complex m), 1.35–1.55 (2 H, complex m), 3.75–3.9 (1 H, m), 4.15 (2 H, q, J = 6 Hz), 4.62–4.7 (1 H, m), 6.35 (1 H, d, J = 6 Hz).

Diazo ketone 6a: prepared the same as **3** from **5a** in 61% yield; IR 2100, 1650, 1375, 1065 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.5–1.7 (1 H, m), 1.8–2.2 (5 H, complex m), 2.5 (2 H, s(b)), 4.72–4.85 (1 H, m), 4.65–4.72 (1 H, m) 5.3 (1 H, s(b)), 6.35 (1 H, d, J = 6 Hz).

Spirocyclic ketone 11: prepared the same as **10** from **6a** to afford crude spirocyclic ketone **11** in 95% yield as an oil; ^1H NMR (250 MHz, C_6D_6) δ 1.05–1.2 (1 H, m), 1.28 (2 H, td, J = 6, 1.5 Hz), 1.3–1.85 (3 H, complex m), 1.85–2.0 (2 H, complex m), 2.25–2.4 (2 H, m), 4.45–4.5 (1 H, m), 6.10 (1 H, d(b), J = 6 Hz).

Preparation of Ethyl 5-(3,4-Dihydro-2*H*-pyran-2-yl)-2-pentanoate (8a). (i) **Ethyl *trans*-5-(3,4-Dihydro-2*H*-pyran-2-yl)-2-pentenoate.** To a solution of ester **5a** (3.03 g, 16.5 mmol) in toluene (20 mL), cooled to −78 °C, was added 1.5 M DIBAL-H in toluene (12 mL, 18 mmol). The mixture was stirred at this temperature for 2 h, quenched with 1 N HCl, and extracted with toluene. The organic layers were dried and evaporated to dryness to afford the corresponding aldehyde.

The crude aldehyde was dissolved in toluene (50 mL) and (carboethoxymethylene)triphenylphosphorane (6.0 g, 17.2 mmol) was added. The mixture was stirred at 40 °C for 2 h. Then the reaction mixture was evaporated to dryness under vacuum and flash chromatographed on silica gel, eluting with 10% EtOAc/hexane to afford the trans olefin as the major compound (2.08 g, 60%): IR 1720, 1650 cm^{-1}. Trans olefin: ^1H NMR (250 MHz, $CDCl_3$) δ 1.3 (3 H, t, J = 6 Hz), 1.55–1.9 (6 H, complex m), 1.95–2.10 (2 H, complex m), 2.25–2.4 (2 H, complex m), 3.72–3.85 (1 H, m), 4.18 (2 H, q, J = 6 Hz), 4.65–4.72 (1 H, m), 5.85 (1 H, dd, J = 16, 2 Hz), 6.35 (1 H, d(b), J = 6 Hz), 6.95–7.05 (1 H, m).

(ii) **Ester 8a.** A mixture of triethylsilane (2.1 mL, 13.1 mmol) and the α,β-unsaturated ester (2.5 g, 11.9 mmol) was heated at 100 °C for 10 min in the presence of Wilkinson's catalyst ($(Ph_3P)_3RhCl$, 35 mg). The residue was flash chromatographed on flash silica gel, eluting with 10% EtOAc/hexane to afford the ester **8a** (1.85 g, 74%): IR 1740, 1650, 1235, 1180, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (3 H, t, J = 6 Hz), 1.4–1.9 (8 H, complex m), 1.95–2.1 (2 H, complex m), 2.3 (2 H, t, J = 6 Hz), 3.7–3.8 (1 H, m), 4.1 (2 H, q, J = 6 Hz), 4.65 (1 H, dt, J = 6, 3 Hz), 6.35 (1 H, dt, J = 6, 3 Hz).

Diazo ketone 9a: prepared the same as **3** from **8a** in 30% yield; IR 2100, 1650, 1370, 1065 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.4–1.9 (8 H, complex m), 1.9–2.1 (2 H, complex m), 2.35 (2 H, t), 3.7–3.8 (1 H, m), 4.6–4.7 (1 H, m), 5.2 (1 H, s(b)), 6.35 (1 H, d, J = 6 Hz).

3-(3,4-Dihydro-2*H*-pyran-2-yl)cyclohexanone (15): prepared the same as **10** from **9a** but flash chromatographed on silica gel, eluting with 15% EtOAc/hexane (41 mg, 91%, 1:1 mixture of diasteromers); IR 1740, 1160, 1030 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.5–2.5 (13 H, complex m), 3.75–3.95 (1 H, m), 4.6–4.7 (1 H, m), 6.35 (1 H, d, J = 6 Hz); ^{13}C NMR (250 MHz, $CDCl_3$) δ 219.3 and 219.1, 143.6, 100.4, 73.6 and 73.4, 45.7 and 45.0, 41.1 and 41.2, 38.5 and 38.3, 33.8 and 33.7, 30.0 and 29.5, 28.3, 19.7; MS exact mass calcd for $C_{11}H_{17}O_2$ (M^+ + 1) 181.123, found 181.123.

Preparation of Ethyl 3-(3,4-Dihydro-2-methyl-2*H*-pyran-2-yl)-propanoate (5b): (i) **Ethyl (*trans* and *cis*)-3-(3,4-Dihydro-2-methyl-2*H*-pyran-2-yl)acrylate**: prepared the same as ethyl (*trans* and *cis*)-3-(3,4-dihydro-2*H*-pyran-2-yl)acrylate, from 3,4-dihydro-2-methyl-2*H*-pyran-2-carboxaldehyde (**4b**) to afford trans olefin (15.1 g, 81%) and cis olefin (1.7 g, 9%) as oils. Trans olefin: IR 1740, 1650, 1305, 1240, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.3 (3 H, t, J = 6 Hz), 1.35 (3 H, s), 1.7–1.85 (2 H, m), 1.85–2.0 (2 H, m), 4.2 (2 H, q, J = 6 Hz), 4.65–4.7 (1 H, m), 5.95 (1 H, d, J = 16 Hz), 6.35 (1 H, d, J = 6 Hz), 6.82 (1 H, d, J = 16 Hz). Cis olefin: IR 1740, 1650, 1420, 1190, 1055 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.3 (3 H, t, J = 6 Hz), 1.35 (3 H, s), 1.7–1.85 (2 H, m), 1.85–2.2 (2 H, m), 4.2 (2 H, q, J = 6 Hz), 4.65–4.71 (1 H, m), 5.75 (1 H, d, J = 6 Hz), 6.3 (1 H, d, J = 9 Hz), 6.4–6.5 (1 H, m).

(ii) **Ester 5b**: prepared the same as **5a** from the corresponding α,β-unsaturated ester in 81% yield; IR 1740, 1650, 1240, 1180 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.2 (3 H, s), 1.25 (3 H, t, J = 6 Hz), 1.6–1.85 (3 H, complex m), 1.95–2.1 (3 H, complex m), 2.4 (2 H, t, J = 6 Hz), 4.15 (2 H, q, J = 6 Hz), 4.6–4.7 (1 H, m), 6.25 (1 H, d, J = 6 Hz).

Diazo Ketone 6b: prepared in 75% yield the same as **3** and **5b**; IR 2100, 1650, 1380, 1065 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.2 (3 H, s), 1.55–1.85 (3 H, complex m), 1.9–2.1 (3 H, complex m), 2.45 (2 H, t), 4.6–4.7 (1 H, m), 5.3 (1 H, s(b)), 6.25 (1 H, d, J = 6 Hz).

Oxa-tricyclic ketone 13: prepared the same as **10** from **6b** to afford crude tricyclic in 95% yield (95% pure by ^1H NMR) as an oil; IR 1665, 1350, 1240, 1210, 1090, 870 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 0.65–0.78 (1 H, m), 0.80–1.0 (2 H, m), 0.98 (3 H, s), 1.05–1.3 (2 H, complex m), 1.5–1.7 (2 H, complex m), 1.78 (1 H, t, J = 6 Hz), 2.15 (1 H, td, J = 12, 3 Hz), 2.5 (1 H, dt, J = 12, 3 Hz), 3.65 (1 H, t, J = 6 Hz); ^{13}C NMR (250 MHz, $CDCl_3$) δ 205.1, 73.3, 56.6, 42.0, 35.9, 33.1, 32.5, 29.3, 15.8, 13.9; MS, exact mass calcd for $C_{10}H_{15}O_2$ (M^+ + 1) 167.107, found 167.107.

Preparation of Diazo Ketone 7. (i) **Methyl 4-(3,4-dihydro-2-methyl-2*H*-pyran-2-yl)butanoate**: prepared the same as methyl 3,4-dihydro-2H-pyran-2-acetate from **6b** in 89% yield; ^1H NMR (250 MHz, $CDCl_3$) δ 1.15 (3 H, s), 1.4–1.75 (6 H, complex m), 1.9–2.0 (2 H, m), 2.30 (2 H, t, J = 3 Hz), 3.7 (3 H, s), 4.60 (1 H, dt, J = 6, 3 Hz), 6.25 (1 H, dt, J = 6, 2 Hz).

(ii) **Diazo ketone 7**: prepared the same as **3** from the corresponding ester to afford diazo ketone in 40% yield as an oil; IR 2100, 1650, 1375, 1065 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.2 (3 H, s), 1.45–1.75 (6 H, complex m), 1.9–2.0 (2 H, m), 2.3 (2 H, t), 4.55–4.62 (1 H, m), 5.25 (1 H, s(b)), 6.2 (1 H, d(b), J = 6 Hz).

Oxa-tricyclic ketone 14: prepared the same as **10** from **7** to afford crude **14** in 80% yield as an oil; IR 1675, 1240, 1175, 1165, 1080 cm^{-1}; ^1H NMR (250 MHz, C_6D_6) δ 0.8–0.95 (1 H, m), 1.0–1.7 (9 H, complex m), 1.05 (3 H, s), 2.3–2.45 (1 H, m), 2.82 (1 H, td, J = 9, 3 Hz), 3.4 (1 H, t, J = 6 Hz); ^{13}C NMR (250 MHz, $CDCl_3$) δ 210.3, 71.8, 51.5, 43.0, 40.1, 32.7, 30.2, 29.9, 21.0, 15.1, 13.2; MS, exact mass calcd for $C_{11}H_{17}O_2$ (M^+ + 1) 181.123, found 181.123.

Preparation of Ethyl 5-(3,4-Dihydro-2-methyl-2*H*-pyran-2-yl)pentanoate (8b). (i) **Ethyl *trans*-5-(3,4-dihydro-2-methyl-2*H*-pyran-2-yl)-2-pentenoate**: prepared the same as ethyl *trans*-5-(3,4-dihydro-2*H*-pyran-2-yl)-2-pentenoate from **5b** to afford trans olefin (as major compound) in 70% yield as an oil. Trans olefin: ^1H NMR (250 MHz, $CDCl_3$) δ 1.2 (3 H, s), 1.28 (3 H, t, J = 6 Hz), 1.5–1.9 (4 H, complex m), 1.95–2.1 (2 H, m), 2.25–2.4 (2 H, m), 4.2 (2 H, q, J = 6 Hz), 4.6–4.68 (1 H, m), 5.8 (1 H, dd, J = 16, 2 Hz), 6.3 (1 H, d(b), J = 6 Hz), 6.9–6.95 (1 H, m).

(ii) **Ester 8b**: prepared as **5a** from the corresponding α,β-unsaturated ester to afford **8b** in 98% as an oil; IR 1740, 1650, 1240, 1180, 1070 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.2 (3 H, s), 1.28 (3 H, t, J = 6 Hz), 1.35–1.5 (2 H, m), 1.5–1.75 (6 H, complex m), 1.95–2.05 (2 H, m), 2.32 (2 H, t, J = 6 Hz), 4.15 (2 H, q, J = 6 Hz), 4.62 (1 H, dt, J = 6, 3 Hz), 6.28 (1 H, dt, J = 6, 3 Hz).

Diazo ketone 9b: prepared the same as **3** from **8b** to afford **9b** in 26% yield as an oil; ^1H NMR (250 MHz, $CDCl_3$) δ 1.2 (3 H, s), 1.3–1.5 (2 H, m), 1.5–1.75 (6 H, complex m), 1.9–2.0 (2 H, m), 2.35 (2 H, t), 4.6–4.7 (1 H, m), 5.25 (1 H, s(b)), 6.25 (1 H, d, J = 6 Hz).

3-(3,4-Dihydro-2-methyl-2*H*-pyran-2-yl)cyclohexanone (16): prepared the same as **10** from **9b** to afford **16** in 84% yield as an oil, as a 1:1 mixture of diastereomers; IR 1740, 1650; ^1H NMR (250 MHz, C_6D_6) δ 0.8–2.0 (13 H, complex m), 4.48–4,5 (1 H, m), 6.25 (1 H, dd, J = 6 Hz); MS 194 (M^+), 123, 97, 83 (cyclopentanone$^+$), 55, 41.

***syn*-5-Formyl-2-hydroxycyclohexanone (18).** A solution of oxa-tricyclic ketone **2** (60 mg, 0.48 mmole) in THF (3 mL) was treated with *p*-toluenesulfonic acid monohydrate (91 mg, 0.48 mmole) for 30 min at room temperature. The reaction mixture was quenched with 25% aqueous ammonium acetate, extracted with ether, dried over Na_2SO_4, and evaporated to dryness to give product **18** (66 mg, 98%): ^1H NMR (250 MHz, $CDCl_3$) δ 1.6–2.6 (6 H, complex m), 3.0 ($^1/_2$ H, dt, J = 12, 1.5 Hz), 3.1–3.18 ($^1/_2$ H, m), 4.1 (1 H, dd, J = 12, 3 Hz), 9.65 (1 H, s). ^{13}C NMR (250 MHz, $CDCl_3$) 208.2, 201.4, 74.8, 48.7, 37.2, 31.9, 21.8; MS 142 (M^+), 124, 100, 99, 84, 83, 82.

Lactone 21. The hemiacetal **19** was prepared in the same manner as **18** from **10** in 100% yield and used as is.

To a solution of hemiacetal **19** (111 mg, 0.71 mmol) in CH_2Cl_2 (3 mL) were added anhydrous sodium acetate (15 mg, 0.18 mmol) and pyridinium chlorochromate (305 mg, 1.42 mmol), and the mixture was stirred at room temperature for 3 h. The reaction mixture was diluted with ether, triturated (3×), and filtered through a small plug of silica gel. The filtrate was evaporated and the obtained solid was recrystallized from ether to afford lactone **21** (91 mg, 82%): mp 112–112.5 °C; IR 1750, 1710, 1350, 1265, 1145, 1070, 1020 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.95 (2 H, d, J = 6 Hz), 2.15–2.35 (2 H, m), 2.7–2.9 (3 H, complex m), 3.0–3.1 (2 H, m), 4.85–4.9 (1 H, m); MS, exact mass calcd for $C_8H_{14}O_3N$ (M^+ + 1 + NH_3) 172.097, found 172.097.

Anal. Calcd for $C_8H_{10}O_3$: C, 62.32; H, 6.54. Found: C, 62.52; H, 6.61.

Lactone 22: prepared the same as **21** from **13** to afford **22** in 85% yield, as a white solid: mp 74–75 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.5 (3 H, s), 1.70–2.2 (6 H, complex m), 2.4 (1 H, dt, J = 9, 3 Hz), 2.55–2.72 (2 H, m), 2.98 (1 H, dd, J = 9, 3 Hz), 3.0–3.1 (1, H, m); ^{13}C NMR (250 MHz, $CDCl_3$) δ 211.4, 175.0, 82.1, 49.4, 41.4, 37.1, 36.0, 32.1, 29.5, 22.8; MS, exact mass calcd for $C_{10}H_{15}O_3$ (M^+ + 1) 183.102, found 183.102.

Lactol aldehyde 24: prepared the same as **18** from **14** to afford **24** in crude yield 80% (crude **24** could be flash chromatographed on silica gel, eluting with 40% EtOAc/hexane); IR 1720, 1080 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 1.1 (3 H, s), 1.3–1.45 (4 H, m), 1.65–1.75 (2 H, complex m), 1.8–2.0 (4 H, complex m), 2.2 (2 H, qd, J = 12, 3 Hz), 2.65–2.75 (1 H, m), 4.8 (1 H, s), 9.7 (1 H, s); ^{13}C NMR (250 MHz, $CDCl_3$) δ 205.6, 96.6, 73.8, 46.2, 35.1, 34.5, 34.2, 31.5, 29.8, 18.3, 18.2; MS, exact mass calcd for $C_{11}H_{17}O_2$ (M^+ + 1 − H_2O) 188.123, found 181.123.

Lactol acid 25: mp 153–154 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.25 (3 H, s), 1.3–1.6 (4 H, complex m), 1.7–2.25 (7 H, complex m), 2.35 (1 H, dd, J = 12, 3 hZ), 2.85–3.0 (1 H, m), 6.2–7.1 (2 H, broad singlet exchangeable).

Bis(thiolactol) 26. To a solution of oxa-tricyclic ketone **13** (50 mg, 0.36 mmol) and 1,2-ethanedithiol (75 μL, 0.90 mmol) in anhydrous CH_2Cl_2 (1 mL) was added boron trifluoride etherate (2% equiv) at room temperature, the mixture was stirred for 10 min, and the reaction was quenched with 25% aqueous ammonium acetate. The mixture was extracted with CH_2Cl_2, dried, and evaporated. The residue was flash chromatographed on silica gel, eluting with 20% EtOAc/hexane to afford **26** (59 mg, 53%): ^1H NMR (250 MHz, $CDCl_3$) δ 1.65 (1 H, s(b),

exchangeable), 1.8–2.1 (5 H, complex m), 2.1–2.6 (4 H, complex m), 3.15–3.3 (4 H, m), 3.4 (4 H, t, J = 1.5 Hz), 4.0 (1 H, t), 4.58 (1 H, d, J = 3 Hz); MS, exact mass calcd for $C_{12}H_{21}OS_4$ (M^+ + 1) 309.048, found 309.047.

Keto Thiolactol 27. To a solution of oxa-tricyclic ketone **13** (50 mg, 0.36 mmol) and 1,2-ethanedithiol (30 μL, 0.36 mmol) in THF (1 mL) was added at −78 °C 1 M $ZnCl_2$ in THF (2% equiv). The mixture was slowly warmed to −10 °C, the reaction was quenched with 25% aqueous ammonium acetate, and the solution was extracted with Et_2O. The organic layer was dried and evaporated. The residue was flash chromatographed on silica gel, eluting with 20% EtOAc/hexane to afford **27** (53 mg, 64%) as an oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.65–1.8 (3 H, complex m), 2.1–2.25 (1 H, m), 2.3–2.42 (1 H, m), 2.6 (1 H, dd, J = 14, 2 Hz), 2.7–3.1 (8 H, complex m), 4.25 (1 H, s(b)), 5.4 (1 H, s(b)).

Ketone 28. To a solution of **27** (23 mg, 0.10 mmol) in CH_2Cl_2 (1 mL) was added, at room temperature, boron trifluoride etherate (2% equiv) and the solution was stirred for 10 min. The mixture was quenched with 25% aqueous ammonium acetate, extracted with CH_2Cl_2, dried, and evaporated to afford **28** (20 mg, 87%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.6 (1 H, s(b), exchangeable), 1.65–1.9 (4 H, complex m), 2.0–2.15 (1 H, m), 3.5 (1 H, dd, J = 12, 9 Hz), 3.65 (1 H, dd, J = 12, 3 Hz), 3.7–3.85 (2 H, m), 3.15 (4 H, s(b)), 4.2 (1 H, t), 4.52 (1 H, d, J = 4 Hz); MS, exact mass calcd for $C_{10}H_{17}O_2S_2$ (M^+ + 1) 233.067, found 233.067.

Ketone 29a. A solution of oxa-tricyclic ketone **14** (358 mg, 2.18 mmol) and 1,2-ethanedithiol (0.21 mL, 2.18 mmol) in THF (6 mL) was cooled to −78 °C and $TiCl_4$ (5 μL, 0.044 mmol) added. The mixture was warmed to room temperature for 30 min and finally heated to 50 °C for 48 h. The reaction mixture was quenched with 25% aqueous ammonium acetate, extracted with ether, dried, and evaporated. The residue was flash chromatographed on silica gel, eluting with 40% EtOAc/hexane to afford **29a** (460 mg, 82%) (substantial amount of hemiacetal **29b**): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.35 (3 H, s), 1.4–2.3 (11 H, complex m), 3.0 (1 H, s, exchangeable), 3.15–3.25 (4 H, m), 4.52 (1 H, d, J = 4 Hz); MS, exact mass calcd for $C_{12}H_{19}OS_2$ (M^+ + 1 − H_2O) 243.088, found 243.088.

Registry No. 1, 103668-91-3; **2**, 103668-90-2; **3**, 109390-69-4; **4a**, 100-73-2; **4b**, 26334-42-9; **5a**, 109390-83-2; **5b**, 109390-98-9; **6a**, 109390-85-4; **6b**, 109390-99-0; **7**, 109390-72-9; **8a**, 109390-93-4; **8b**, 109391-02-8; **9a**, 109390-94-5; **9b**, 109391-03-9; **10**, 109390-74-1; **11**, 109390-75-2; **12**, 109390-76-3; **13**, 109390-77-4; **14**, 109390-78-5; (*R**,*R**)-**15**, 109390-79-6; (*R**,*S**)-**15**, 109390-95-6; (*R**,*R**)-**16**, 109390-80-9; (*R**,*S**)-**16**, 109391-04-0; **18**, 109390-81-0; **19**, 109390-82-1; **21**, 70260-40-1; **22**, 109390-84-3; **24**, 109390-86-5; **25**, 109390-87-6; **26**, 109390-88-7; **27**, 109390-89-8; **28**, 109390-90-1; **29a**, 109391-05-1; **29b**, 109391-06-2; $[Rh(OAc)_2]_2$, 15956-28-2; $EtOC(O)CH{=}PPh_3$, 1099-45-2; $HS(CH_2)_2SH$, 540-63-6; methyl 3,4-dihydro-2*H*-pyran-2-acetate, 109390-70-7; sodium 3,4-dihydro-2*H*-pyran-2-acetate, 109390-71-8; ethyl *trans*-3-(3,4-dihydro-2*H*-pyran-2-yl)acrylate, 76919-60-3; ethyl *cis*-3-(3,4-dihydro-2*H*-pyran-2-yl)acrylate, 109390-73-0; 3-(3,4-dihydro-2*H*-pyran-2-yl)propanal, 109390-91-2; ethyl *trans*-5-(3,4-dihydro-2*H*-pyran-2-yl)-2-pentenoate, 109390-92-3; ethyl *trans*-5-(3,4-dihydro-2-methyl-2*H*-pyran-2-yl)-2-pentenoate, 109391-01-7; ethyl *trans*-3-(3,4-dihydro-2-methyl-2*H*-pyran-2-yl)acrylate, 109390-96-7; ethyl *cis*-3-(3,4-dihydro-2-methyl-2*H*-pyran-2-yl)acrylate, 109390-97-8; methyl 4-(3,4-dihydro-2-methyl-2*H*-pyran-2-yl)butanoate, 109391-00-6.

Supplementary Material Available: X-ray crystal structure analysis of **25** and tables of functional coordinates and temperature factors, bond distances, and bond angles for **25** (4 pages). Ordering information is given on any current masthead page.

Local Conformer Effects in Unsaturated Lactones

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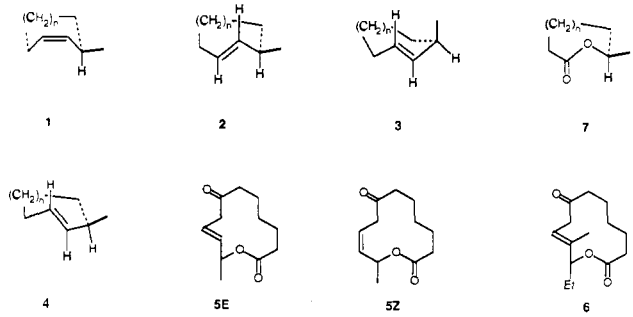
Abstract: Allylic unsaturated lactones **5E** and **5Z** can be epoxidized and osmylated with useful stereocontrol. The epoxidations follow the pattern predicted from evaluation of local conformer effects, and epoxides **8** and **14** are favored. These products correspond to peripheral attack on the exposed olefin face of conformers similar to **1** (*Z*-alkene) or **2** (*E*-alkene). As in the case of simple carbocyclic alkenes, osmylation of the *Z*-isomer (**5Z**) follows the same selectivity pattern as the epoxidation, and **16** is the major diol. However, the isomeric **5E** is osmylated from the opposite olefin face compared to the epoxidation and gives **13** as the major diol. The analysis of epoxidations by the local conformer approach is compared with the results of molecular mechanics (MACROMODEL) evaluations of the favored conformers of **5E** and **5Z** and of the derived epoxides.

In a previous report from this laboratory, the selective epoxidation of 3-methylcycloalkenes in 8–15-membered rings was described.[1] Olefin face preferences were interpreted on the basis of local conformer effects due to the inherent geometric requirements of the ring segment −C=C—C(CH_3)− and its neighboring substituents. Transition-state geometry for the highly selective electrophilic additions to *Z*-alkenes was approximated by the tub-like local conformer **1** having pseudoequatorial methyl. The less selective reactions of disubstituted *E*-alkenes were attributed to transition states resembling the crownlike local geometry **2** with a pseudoequatorial methyl group. The extrapolation from local olefin geometry to transition-state geometry is intuitively simple for cis addition reactions because the bicyclic transition states differ from olefin conformers **1** and **2** by relatively small changes in bond angles and hybridization. As long as the electrophile is compact and does not introduce major new steric interactions, the same factors which favor **1** and **2** (minimized transannular, gauche, and eclipsed interactions) should favor similar transition-state geometries. In the case of MCPBA epoxidations, these conditions are satisfied and even the final epoxide can be expected to prefer a similar local geometry as in **1** or **2**.

Osmylations are significantly less selective then are epoxidations in the medium ring alkenes.[1] Useful selectivity is observed with the *Z*-alkenes, but not in the case of the disubstituted *E*-isomers. This trend was attributed to the steric bulk of the reactive electrophile (OsO_4·L) which might be tolerated better in transition-state geometries with pseudoaxial methyl, derived from olefin local conformer **3**, or in non-crownlike local geometries such as **4**.



(1) Vedejs, E.; Gapinski, D. M. *J. Am. Chem. Soc.* **1983**, *105*, 5058.

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