ion chemical-ionization conditions.[6]

Acknowledgment is made to the U.S. Army Research Office (Grant No. DAAG29-80-C-0101) for their support of this research.

(6) Hunt, D. F.; Crow, F. W. *Anal. Chem.* **1978**, *50*, 1781-1784.

Registry No. Cyclohexanone, 108-94-1; 2-methylcyclohexanone, 583-60-8; 4-*tert*-butylcyclohexanone, 98-53-3; 2-decanone, 693-54-9; 3-decanone, 928-80-3; 4-decanone, 624-16-8; 5-decanone, 820-29-1; 1*H*-indole-3-acetic acid, 87-51-4; abscisic acid, 21293-29-8; gibberellin A_3, 77-06-5.

Communications

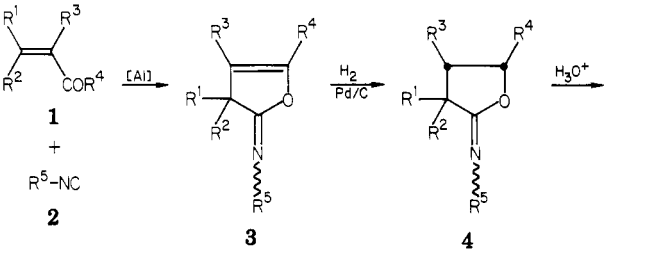
A New Approach for Stereoselective Synthesis of γ-Butyrolactones

Summary: Diethylaluminum chloride promotes 1,4-cycloaddition of α,β-unsaturated carbonyl compounds with isocyanides to afford unsaturated N-substituted iminolactones, which are stereoselectively converted to γ-butyrolactones via hydrogenation on Pd/C and then acid hydrolysis.

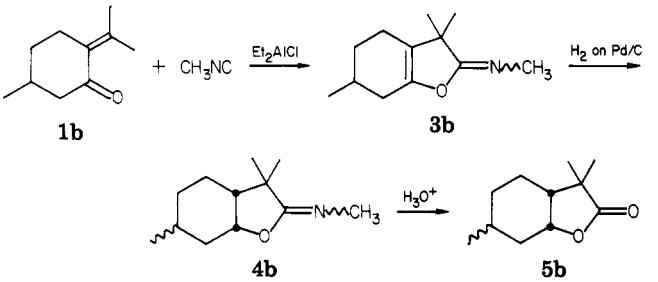
Sir: Recently, an interest in some biologically active sesquiterpenes having a α-methylene-γ-butyrolactone moiety[1] has been intensified, which has rapidly increased needs for the synthetic methods of them. One of the key points of the synthesis is the stereoselective construction of ring-fused γ-butyrolactones.[1] Herein, we report a unique and versatile approach for stereoselective synthesis of ring-fused γ-butyrolactones via Lewis acid catalyzed 1,4-cycloadditions of isocyanides **2** to α,β-unsaturated carbonyl compounds **1**, which lead to unsaturated N-substituted iminolactones **3** as shown in Scheme I. The cycloaddition of isocyanides **2** with α,β-unsaturated carbonyl compounds **1** was most efficiently induced by diethylaluminum chloride and ethylaluminum dichloride,[2] which are also notable catalysts in Snider's work[3] on the reactions of α,β-unsaturated carbonyl compounds with olefins.

A representative procedure for the cycloaddition of isocyanide **2** with α,β-unsaturated carbonyl compound **1** is as follows. To a stirring solution of 730 mg (4.8 mmol) of pulegone (**1b**) and 238 mg (5.8 mmol) of methyl isocyanide in 10 mL of tetrahydrofuran was dropwise added a solution of 0.65 mL (4.81 mmol)[4] of diethylaluminum chloride in 10 mL of tetrahydrofuran at 5–10 °C, and then the mixture was stirred at room temperature for 12 h. The reaction mixture was poured into cold aqueous K_2CO_3 and extracted with ether. The ether extract was evaporated and distilled with a Kugelrohr apparatus to furnish bicyclic unsaturated *N*-methyliminolactone **3b** in 85% yield [**3b**: bp 60–65 °C (0.1 mmHg);[5] IR (neat) 1734, 1702 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.01 (d, 3 H), 1.16 (s, 6 H), 0.7–2.5 (m, 7 H), 3.01 (s, 3 H)]. Some syntheses of unsaturated

Scheme I



N-substituted iminolactones **3** and **6**[6] are summarized in Table I.



The present cycloadditions work well with crowded β,β-disubstituted α,β-unsaturated carbonyl compounds (runs 1–4). Thus, the reaction[7] of 8-methyl-Δ[8]-octal-1-one (**1c**) with *tert*-butyl isocyanide provided tricyclic unsatu-

(1) Grieco, P. A. *Synthesis* **1975**, 67.

(2) The cycloadditions of isocyanides with α,β-unsaturated carbonyl compounds were also promoted by $AlCl_3$ and $BF_3{\cdot}OEt_2$ but with much less efficiency.

(3) Snider, B. B.; Rodini, D. J.; van Straten, J. *J. Am. Chem. Soc.* **1980**, *102*, 5872.

(4) The cycloaddition of isocyanice with α,β-unsaturated carbonyl compound was very sluggish in the presence of 10–20 mol % of diethylaluminum chloride.

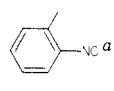
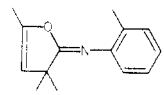
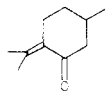
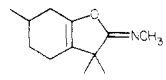
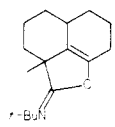
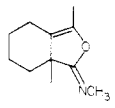
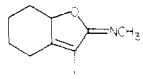
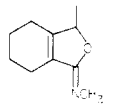
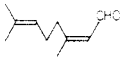
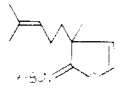
(5) **3b**: Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.81; H, 9.77; N, 7.27.

(6) All new compounds reported gave satisfactory IR and NMR spectra and combustion analyses. Analytical data for selected products are as follows. **3a**: IR (neat) 1725, 1686 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.31 (s, 6 H), 1.75 (d, 3 H, J_{H-H} = 1.3 Hz), 2.06 (s, 3 H), 4.83 (q, 1 H, J_{H-H} = 1.3 Hz), 6.6–7.2 (m, 4 H). Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.23; H, 8.11; N, 6.44. **3c**: IR (neat) 1736, 1708 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.18 (s, 3 H), 1.27 (s, 9 H), 0.7–2.5 (m, 13 H). Anal. Calcd for $C_{16}H_{25}NO$: C, 77.68; H, 10.19; N, 5.66. Found: C, 77.79; H, 9.98; N, 5.90. **6f**: IR (neat) 1687 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.31 (d, 3 H, J_{H-H} = 6.6 Hz), 1.43–2.50 (m, 8 H), 3.04 (s, 3 H), 4.55–5.23 (m, 1 H). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.81; H, 9.03; N, 8.66. **3g**: IR (neat) 1720, 1611 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.17 (s, 3 H), 1.26 (s, 9 H), 1.57 (s, 3 H), 1.64 (s, 3 H), 1.1–2.2 (m, 4 H), 4.83–5.18 (m, 1 H), 5.18 (d, 1 H, J_{H-H} = 3.3 Hz), 6.59 (d, 1 H, J_{H-H} = 3.3 Hz). Anal. Calcd for $C_{15}H_{25}NO$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.60; H, 10.66; N, 5.80.

(7) The reaction was performed by adding slowly *tert*-butyl isocyanide in benzene to a mixture of 1c and diethylaluminum chloride in benzene at 5–10 °C.

0022-3263/82/1947-0741$01.25/0

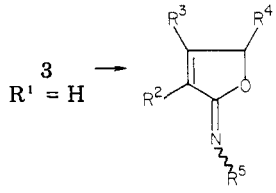
Table I. Synthesis of Unsaturated N-Substituted Iminolactones

run no.	α,β-unsatd carbonyl compd	isocyanide	unsatd N-substituted iminolactone	% yield
1	 1a	 [a]	 3a	79
2	 1b	CH_3NC [b]	 3b	85
3	 1c	*t*-BuNC[a]	 3c	84
4	 1d	CH_3NC[a]	 3d	81
5	 1e	CH_3NC[a]	 6e	80
6	 1f	CH_3NC[a]	 6f	87
7	 1g	*t*-BuNC[a]	 3g	63

[a] Benzene was used as the solvent. [b] THF was used as the solvent.

rated N-*tert*-butyliminolactone **3c** in fairly good yield, which may be converted to the tricyclic lactone that constitutes the basic structure of marrubin and nagilactone.[8]

The cycloadditions with β-monosubstituted α,β-unsaturated carbonyl compounds (runs 5 and 6) afforded α,β-unsaturated N-substituted iminolactones **6**, which may be derived from the isomerization of the initially formed β,γ-unsaturated N-substituted iminolactones **3**.



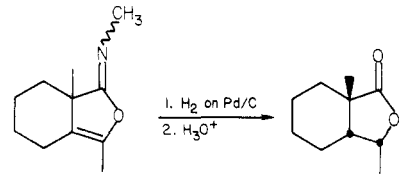
6

As might be expected, the cycloaddition can be successfully carried out only with α,β-unsaturated carbonyl compounds which are capable of assuming a cisoid configuration. The reaction with 2-cyclohexenone which is not capable of assuming such a cisoid configuration afforded a complex mixture of products.

(8) (a) Mangoni, L.; Adinolfi, M. *Tetrahedron Lett.* **1968**, 269. (b) Itô, S.; Kodama, M.; Sunagawa, M. *Tetrahedron Lett.* **1968**, 2065.

Unsaturated N-substituted iminolactones **3** and **6** thus prepared were converted to the corresponding γ-butyrolactones **5** in high yields and high stereoselectivities by hydrogenation on Pd/C and subsequent hydrolysis of the resulting saturated N-substituted iminolactones **4**. For instance, bicyclic β,γ-unsaturated *N*-methyliminolactone **3b** was hydrogenated on 10% Pd/C in acetic acid (10 atm of H_2, 50 °C, 15 h) to afford the corresponding saturated *N*-methyliminolactone **4b** in 83% yield [**4b**: IR (neat) 1710 cm^{-1}; mass spectum, *m/e* 195 (M^+)], which was then hydrolyzed in aqueous oxalic acid (reflux, 24 h) to give cis-fused bicyclic lactone **5b**[9] as a single isomeric product in 80% yield [**5b**: IR (neat) 1764 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.99 (d, 3 H, J_{H-H} = 6.3 Hz), 1.17 (s, 3 H), 1.22 (s, 3 H), 0.6–2.4 (m, 8 H), 4.61 (td, 1 H, J_{H-H} = 6.7 and 6.7 Hz)]. The cis stereochemistry of the ring junction in **5b** was determined by the coupling constants of the NMR signal at 4.61 ppm.

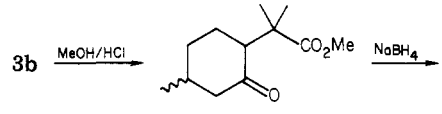
Similarly, bicyclic β,γ-unsaturated *N*-methyliminolactone **3d** was stereoselectively converted to cis-fused bicyclic lactone **5d**[10] in 80% overall yield.



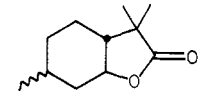
3d **5d**

β,γ-Unsaturated *N*-methyliminolactone **3b** could also be hydrolyzed in hexane–water saturated with oxalic acid to give the corresponding β,γ-unsaturated lactone **7b**[11] in 90% isolated yield (two phases, reflux, 24 h), which was, unexpectedly, very reluctant to hydrogenation on Pd/C under the same reaction conditions employed for the reduction of **3b**.

Synthetic utility of the unsaturated N-substituted iminolactones **3** is further demonstrated by stereoselective transformation to γ-butyrolactones via alcoholysis with HCl followed by reduction of the resultant γ-keto esters **8**, as exemplified by synthesis of trans-fused bicyclic lactone **5b'**[12] (75% overall yield).



8b



5b'

Further studies of stereoselective synthesis of natural products containing the γ-butyrolactone moiety by the present methodology are now in progress in our laboratory.

Registry No. 1a, 141-79-7; **1b**, 89-82-7; **1c**, 80242-75-7; **1d**, 2047-97-4; **1e**, 1122-25-4; **1f**, 932-66-1; **1g**, 5392-40-5; **2** (R^5 = *o*-$C_6H_4CH_3$),

(9) **5b**: Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.33; H, 10.12.

(10) **5d**: IR (neat) 1763 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.25 (s, 3 H), 1.32 (d, 3 H, J_{H-H} = 6.4 Hz), 0.74–2.48 (m, 9 H), 4.75 (qd, 1 H, J_{H-H} = 6.4, 4.2 Hz).

(11) **7b**: IR (neat) 1789 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 0.7–2.38 (m, 7 H), 0.99 (d, 3 H), 1.16 (s, 6 H).

(12) **5b'**: IR (neat) 1772 cm^{-1}; NMR ($CDCl_3$ with Me_4Si) δ 1.03 (d, 3 H, J_{H-H} = 6.7 Hz), 1.07 (s, 3 H), 1.22 (s, 3 H), 0.75–2.4 (m, 8 H), 3.93 (td, 1 H, J_{H-H} = 11.7, 4.7 Hz).

10468-64-1; **2** (R^5 = CH_3), 593-75-9; **2** (R^5 = *t*-Bu), 7188-38-7; **3a**, 80242-76-8; **3b**, 80242-77-9; **3c**, 80242-77-9; **3d**, 80242-79-1; **3g**, 80242-80-4; **4b**, 80242-81-5; **5b**, 80242-82-6; **5d**, 66175-28-8; **6e**, 80242-83-7; **6f**, 80242-84-8; **7b**, 80242-85-9; **8b**, 80242-86-0.

Supplementary Material Available: Experimental details including IR and NMR spectral data and combustion analyses (5 pages). Ordering information is given on any current masthead page.

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Received September 29, 1981

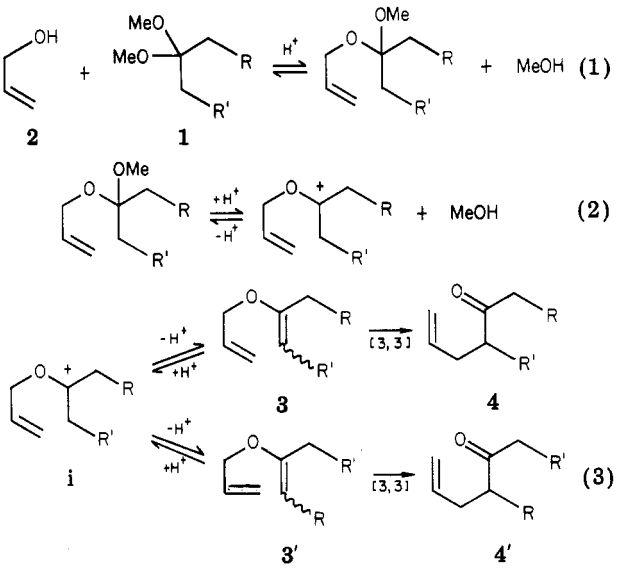
Regioselectivity of the Ketal Claisen Rearrangement[1]

Summary: The ketal Claisen rearrangement with a simple unsymmetrical ketal exhibits a high degree of regioselectivity, which is attenuated by substitution of the α- and β-carbon atoms of the ketal.

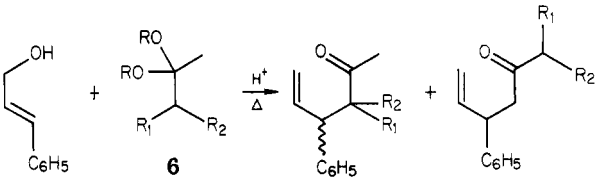
Sir: The Claisen rearrangement has emerged as a very general and powerful synthetic tool over the last 10 years.[2] In particular, enolate Claisen methods,[3] ortho ester/ketal exchange procedures,[4] and amide acetal reactions[5] have provided the synthetic chemist with convenient new methods for exploiting this historically important pathway to α,β-unsaturated carbonyl compounds.

The ketal Claisen rearrangement has only been developed in a few specific cases. The work of Johnson and Faulkner[6-9] provide the only examples of the ketal Claisen rearrangement. The related enol-ether Claisen rearrangements from the work of Saucy[10] are also included in this discussion because they involve nearly identical reaction pathways. For the more general case, the reaction between an acyclic unsymmetrical ketal (**1**) and an allylic alcohol (**2**) can give rise to two isomeric ketonic products. Scheme I details the mechanistic scenario for this process during which the intermediate cation i can be reversibly partitioned along two different pathways. These different paths lead to isomeric allyl/vinyl ethers (**3** and **3'**) which irreversibly ($K_{eq} \simeq 10^6$) rearrange to the isomeric ketones **4** and **4'**. The ketal Claisen rearrangements developed by Johnson and Faulkner specifically avoid this problem, since one of the competing paths in each case is blocked.[11]

Scheme I

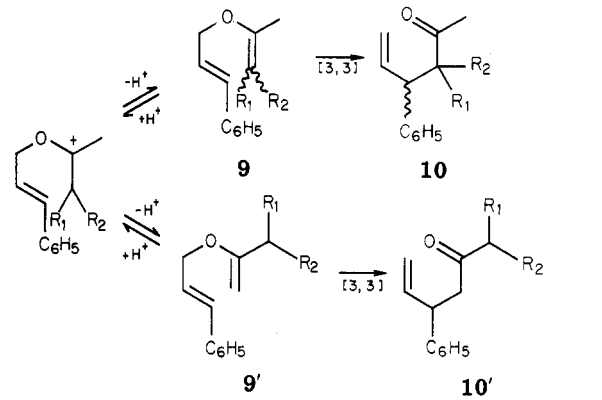


Scheme II



example	R_1	R_2	ketal	% yield	ratio 7:8
a	Me	H	di-Et	63	96:4
b	Et	H	di-Et	66	92:8
c	Et	H	di-Me	84	88:12
d	*i*-Pr	H	di-Et	74	67:33
e	*t*-Bu	H	di-Me	72	0:100
f	*i*-Bu	H	di-Et	62	96:4
g	Me	Me	di-Et	73	69:31
h	Et	Me	di-Me	81	74:26

Scheme III



Recent efforts in our laboratory have been designed to answer this regiochemical question, which is inherent in the ketal Claisen rearrangements of simple unsymmetrical ketals.

Our preliminary work has examined the ketal Claisen rearrangements of some simple unsymmetrical ketals with

(1) Presented in part at the 1981 Pacific Conference on Chemistry and Spectroscopy, Anaheim, Ca Oct 19-21, 1981.
(2) (a) Bennett, G. B. *Synthesis* **1977**, 589. (b) Zeigler, F. E. *Acc. Chem. Res* **1977**, *10*, 227.
(3) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.
(4) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Peterson, M. R. *J. Am., Chem. Soc.* **1970**, *92*, 741.
(5) Felix, D.; Geschwend-Steen, K.; Wick, A. E.; Eschenmoser, A. *Helv. Chim. Acta* **1969**, *52*, 1030.
(6) (a) Werthemann, L.; Johnson, W. S. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, 67, 1465, 1810. (b) Loew, P.; Johnson, W. S. *J. Am. Chem. Soc.* **1971**, 93, 3765.
(7) Johnson, W. S.; Brocksom, T. J.; Loew, P.; Rich, D. H.; Werthemann, L.; Arnold, R. A.; Li, T.; Faulkner, D. J. *J. Am. Chem. Soc.* **1970**, *92*, 4463.
(8) Faulkner, D. J.; Peterson, M. R. *J. Am. Chem. Soc.* **1971**, *93*, 3766.
(9) Johnson, W. S.; Daub, G. W.; Lyle, T. A.; Niwa, M. *J. Am. Chem. Soc.* **1980**, *102*, 7800.
(10) Saucy, G.; Marbet, R. *Helv. Chim. Acta* **1967**, *50*, 2091.

(11) The three examples reported by Johnson and Faulkner (ref 6-8) lack hydrogens on one of the adjacent carbon atoms. The other example reported by Johnson (ref 9) effectively blocks the competing reaction path with a cyclopropyl group, which precludes the formation of an sp^2 carbon atom at one of the α sites. Saucy's enol ether (ref 10) is symmetrical.

0022-3263/82/1947-0743$01.25/0