Table I. Temperature Dependence of ^{13}C Chemical Shifts[a]

carbon	Hz/°C	ref
hydrocarbon[b]	0.2	Me_4Si (^{13}C)
acetone CH_3[c,d]	0.26	CD_3OD (^2H)
acetone CO[e]	0.66	CD_3OD (^2H)
acetone CO[f]	0.99	CCl_4 (^{13}C)
CH_3I[g,h]	1.31	Me_4Si (^{13}C)
CH_2I_2[g,i]	2.35	cyclooctane (^{13}C)

[a] Converted to 50.3 MHz. Each value is not the absolute change in chemical shift with temperature but relative to the temperature dependence of the chemical shift of the internal reference (and nucleus) shown in the column labeled ref. [b] Typical value measured at -43 °C, taken from: Schneider, H.-J.; Freitag, W. *J. Am. Chem. Soc.* **1976**, *98*, 478-481. [c] Allerhand, A., unpublished results. [d] Measured in the range 21-27 °C. [e] Measured in the range 21-35 °C. [f] Measured in the range -80 to 90 °C, taken from Led, J. J.; Petersen, B. *J. Magn. Reson.* **1978**, *32*, 1-17. [g] Taken from Vidrine, D. W.; Peterson, P. E. *Anal. Chem.* **1976**, *48*, 1301-1303. [h] Measured in the temperature range -9 to 1°C. [i] Measured in the temperature range 33-42 °C.

conventional high-resolution NMR.

In this paper we have used the nonprotonated carbon of toluene to demonstrate the feasibility of ultrahigh resolution NMR. However, a nonprotonated carbon does not place a severe requirement on proton-decoupling efficiency. In a separate report[8] we will show that WALTZ-16 proton decoupling, developed by Freeman and co-workers,[7] is an extraordinarily effective low-power proton-decoupling method for ultrahigh resolution NMR.

It would not have been practical to develop ultrahigh resolution NMR at an earlier time. First, without very efficient proton decoupling such as WALTZ-16, residual broadening from ^1H scalar coupling and large temperature gradients caused by high decoupling power levels were the limiting factors.[5] Furthermore, ultrahigh *digital* resolution over the full range of ^{13}C chemical shifts requires data blocks of 256K (and more) points, which would have been prohibitive until recently. What are the advantages of ultrahigh resolution over conventional high-resolution NMR? In general, one expects not only improvements in resolution but also higher signal-to-noise ratios when the instrumental contribution to the line width diminishes.[9,10] The degree of signal-to-noise improvement is dependent on too many parameters for discussion in this paper.[9,10] The degree of resolution improvement depends mainly on the value of the natural line width (W_0). For small molecules such as toluene, with $W_0 \lesssim 30$ mHz ($T_1 \gtrsim 10$ s), going from $W_{in} = 200$ to 10 mHz will yield an improvement in resolution of a factor $\gtrsim 6$, equivalent to going from a 200-MHz (^1H) spectrometer to a 1200-MHz spectrometer under conventional high-resolution conditions. For larger molecules the advantage is smaller but still very significant. On the basis of published T_1 values,[11] we expect W_0 in the range 0.1-1.0 Hz for the ^{13}C resonances of most molecules up to the size of steroids. At the lower end of this range, the improvement is resolution is a factor of about 3 when going from $W_{in} = 0.2$ to 0.01 Hz. At the upper end the resolution improvement is only about 20%, comparable to the expected improvement when going from 500 (^1H) to 600 MHz. Furthermore, in ultrahigh resolution NMR of large molecules (with $W_0 \gtrsim 0.5$ Hz) we have $W_{ex} = W_0$ to a very good approximation and, since $W_0 = 1/\pi T_2$, the observed line widths in a single spectrum may yield accurate T_2 values for each resonance.[12]

Acknowledgment. This work was supported by the Natonal Science Foundation (PCM 83-04699) and the National Institutes of Health (GM 22620).

(8) Allerhand, A.; Addleman, R. E.; Osman, D.; Dohrenwend, M. *J. Magn. Reson.*, in press.
(9) Waugh, J. S. *J. Mol. Spectrosc.* **1970**, *35*, 298-305.
(10) Martin, M. L.; Martin, G. J.; Delpuech, J.-J. "Practical NMR Spectroscopy"; Heyden: London, 1980.
(11) Allerhand, A.; Doddrell, D.; Komoroski, R. *J. Chem. Phys.* **1971**, *55*, 189-197.
(12) Allerhand, A.; Dohrenwend, M. *J. Am. Chem. Soc.*, in press.

Tandem Electrocyclic-Sigmatropic Reaction of Benzocyclobutenes. An Expedient Route to 4,4-Disubstituted Isochromanones

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Previous results[1] from our laboratory have demonstrated that the thermolysis of 1-acyl-1-alkylbenzocyclobutenes provides an efficient route to substituted isochromenes through a predominant electrocyclic reaction (ECR). In particular, upon thermolysis of the carboxylic acid **1**, the 4-alkylisochroman-3-one **4** could be obtained via the *Z* conformer of the *o*-quinodimethane **2** in a quantitative yield (Scheme I).

This reaction suggested that the ketene hemiacetal **3**[2] should intervene in the conversion. Assuming that the C_3-OH in **3** can be substituted for allyoxy group, the resulting ketene acetal[3] (**6**) seems to undergo spontaneous [3,3]-sigmatropic reaction[4] (STR). To this purpose, the starting material should be the allyl ester **5** which would easily be accessible from the corresponding allyl alcohol and the carboxylic acid. From a practical point of view, since the resulting isochroman-3-one **7** has the quaternary carbon on a benzyl position, this strategy seems to provide an efficient route to a promising synthon for several types of natural products such as Amaryllidaceae alkaloids[5] or alkaloids of the Calabar bean.[6] (Scheme II).

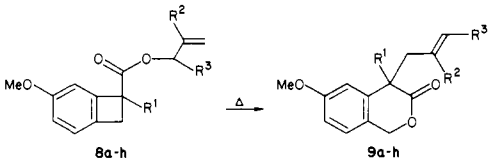
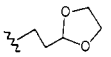
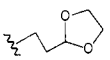
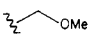
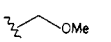
In this paper we report a convenient method for constructing 4,4-disubstituted isochromanones via an unprecedented tandem electrocyclic-sigmatropic reaction of benzocyclobutenes.

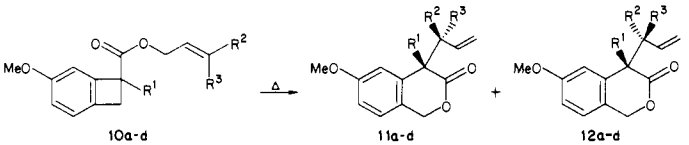
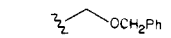
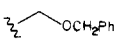
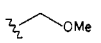
The required substrates for the thermolysis were prepared from readily available 1-cyano-5-methoxybenzocyclobutene[7] by a three-step sequence. Alkylation (RX, LDA, HMPA, THF, -78 °C), hydrolysis (KOH, aqueous EtOH, 100 °C), and esterification (the alcohols, DCC, 4-DMAP, CH_2Cl_2, room temperature) yielded the corresponding esters in 80% overall yield. The thermolyses (Tables I-III) were typically carried out in a 0.03-0.05 M *o*-dichlorobenzene[8] solution heated at a bath temperature of 180 °C under an atmosphere of argon. The progress of the reaction was monitored by TLC analysis, and the reaction was cleanly completed within a few hours providing the expected isochroman-3-one[9] via a tandem ECR-[3,3]STR in excellent yield. As indicated by the representative examples in Table I, various allyl esters behave in a similiar fashion, but only in the case of C_1-methoxymethyl (entries 5, 6, and 12 in Table I and entry 3

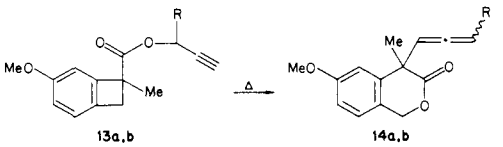
(1) Shishido, K.; Ito, M.; Shimada, S.; Fukumoto, K.; Kametani, T. *Chem. Lett.* **1984**, 1943 and references therein.
(2) Kametani, T.; Enomoto, Y.; Takahashi, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2836.
(3) For the first example of a [3,3]-sigmatropic rearrangement of a ketene acetal, see: Wick, A. E.; Felix, D.; Steen, K.; Eschenmoser, A. *Helv. Chim. Acta* **1964**, *47*, 2425.
(4) For reviews, see: Rhoads, S. J.; Raulins, N. R. *Org. React. (N. Y.)* **1975**, *22*, 1. Ziegler, F. E. *Acc. Chem. Res.* **1977**, *10*, 227. Bennett, G. B. *Synthesis* **1977**, 589.
(5) For a review, see: Sainsbury, M. "Rodd's Chemistry of Carbon Compounds"; Coffey, S., Ed.; Elsevier: Amsterdam, 1975; Vol. IVB, p 165.
(6) For a review, see: Robinson, B. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1971; Vol. XIII, p 213.
(7) Kametani, T.; Kajiwara, M.; Fukumoto, K. *Chem. Ind. (London)* **1973**, 1165; *Tetrahedron* **1974**, *30*, 1053.
(8) The solvent was distilled under reduced pressure and degassed before use.
(9) All new compounds gave satisfactory spectral and analytical (combustion and/or high-resolution mass spectral) data consistent with the structures shown.

0002-7863/85/1507-5810$01.50/0

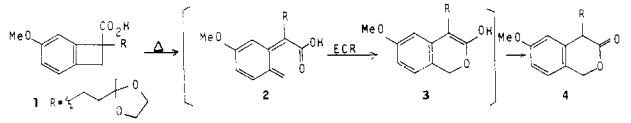
Table I. Tandem Electrocyclic-[3,3]-Sigmatropic Reaction

entry	benzocyclobutene	R^1	R^2	R^3	reaction time, h	product (ratio)	isolated yield, %
							
		8a-h				9a-h	
1	8a	Me	H	H	2	9a	100
2	8b		H	H	5	9b	91
3	8c	Me	Me	H	2	9c	95
4	8d		Me	H	5	9d	98
5	8e		H	H	8	9e + 15a (11:1)	99
6	8f		Me	H	8	9f + 15b (11:1)	100
7	8g	Me	H	*p*-methoxyphenyl	2	9g	70
8	8h	Me	H	$(CH_2)_5Me$	3	9h	98

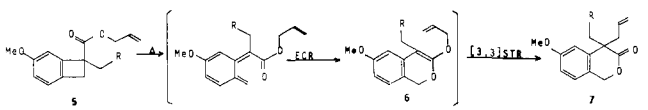
entry	benzocyclobutene	R^1	R^2	R^3	reaction time, h	product ratio, 11:12	isolated yield, %
							
		10a-d			11a-d	12a-d	
9	10a	Me	Me	H	2	3:1	99
10	10b	Me		H	3	5:1	86
11	10c	Me	H		2.5	1:6	86
12	10d		Me	H	9	8:5:1 (15c)	98

entry	benzocyclobutene	R	reaction time, h	product	isolated yield, %
					
	13a,b			14a,b	
13	13a	H	2	14a	95
14	13b	Me	1.5	14b[18]	94

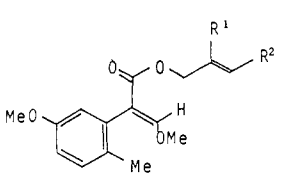
Scheme I



Scheme II



in Table III), has it been found that a competitive [1,5]STR, via (*E*)-*o*-quinodimethane, slightly occurs to some extent to afford **15a-d**[10] stereoselectively.



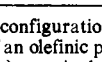
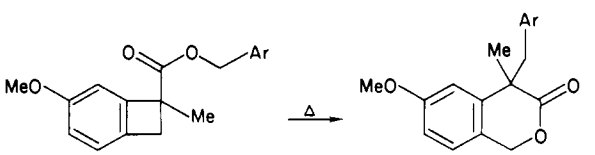
15a $R^1 = R^2 = H$
b $R^1 = Me$, $R^2 = H$
c $R^1 = H$, $R^2 = Me$
d $R^1 + R^2 =$ 

Table II. Tandem Electrocyclic-[1,3]-Sigmatropic Reaction



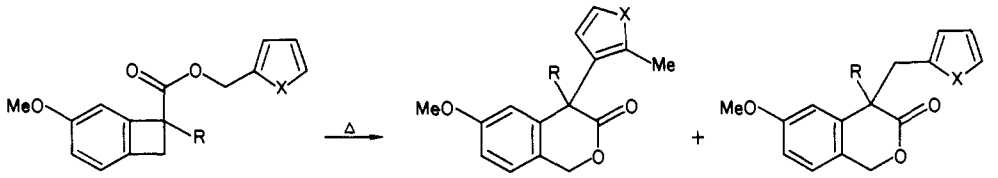
17a-c **18a-c**

entry	benzocyclobutene	Ar	reaction time, h	product	isolated yield, %
1	**17a**	phenyl	2	**18a**	54
2	**17b**	*p*-methoxyphenyl	3	**18b**	46
3	**17c**	2-pyridyl	2	**18c**	53

The (*E*)-alkenes **9g,h** were the exclusive products derived from the secondary allyl esters **8g,h**. Concerning the stereochemical

(10) The *E* configuration of the olefin might be suggested from the chemical shift of an olefinic proton at δ 7.52 (for **15a** and **15d**), 7.53 (for **15b**), and 7.50 (for **15c**) as a singlet. (Calcd value for *E* isomer, 7.51; for *Z* isomer, 7.39).

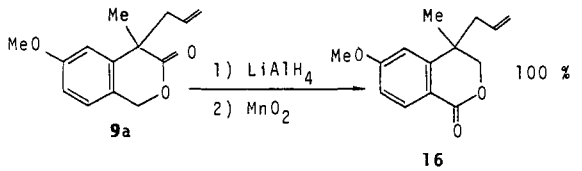
Table III. Competitive Tandem Electrocyclic–Sigmatropic Reaction



19a-c 20a-c 21a-c

entry	benzocyclobutene	R	X	reaction time, h	product ratio **20**:**21**	isolated yield, %
1	**19a**	Me	O	2	1:2	73
2	**19b**	Me	S	3.5	1:5	49
3	**19c**		O	3	3:7:1 (**15d**)	62

Scheme III



9a **16**

features (entries **9–12**, Table I) two possible diastereomers could be formed stereoselectively. The [3,3]STR was highly stereoselective, the major isomer presumably arising through the chair transition state.[11]

The isochroman-3-one (**9a**) thus obtained was easily converted to **16** in a quantitative yield by sequential $LiAlH_4$ reduction and MnO_2 oxidation, the present method also implies a general synthetic route to 4,4-disubstituted isochroman-1-ones (Scheme III).

During the thermolysis of the benzyl esters **17a–c**, the [3,3]STR involving the aromatic ring did not occur,[12,15b] but rather the isochromanones **18a–c**[13] were produced via a tandem ECR–[1,3]STR[14,15] (Table II).

Encouraged by these observations, we also studied the thermolysis of benzocyclobutenes incorporating five-membered heteroaromatics,[16] i.e., furan and thiophene, in the ester part. The products formed were **20** and **21**, which formed through a tandem ECR–[3,3]STR and ECR–[1,3]STR, respectively[17] (Table III).

In these conversions, a preferential formation of the product arising from ECR–[1,3]STR could be observed.

Thus, we have developed a novel and useful tandem technology for the construction of isochromanones with a quaternary center at the benzylic carbon. Application of this methodology to natural product syntheses will be reported in due course.

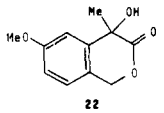
Acknowledgment. We thank Professor D. Seebach, ETH, for valuable discussions on the reaction mechanism.

(11) Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, *18*, 69. Vitorelli, P.; Hansen, H.-J.; Schmid, H. *Helv. Chim. Acta* **1975**, *58*, 1293. Hansen, H.-J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959. Hill, R. K.; Gilman, N. W. *Tetrahedron Lett.* **1967**, 1421; *J. Chem. Soc., Chem. Commun.* **1967**, 619. Faulkner, D. J.; Petersen, M. R. *Tetrahedron Lett.* **1969**, 3243.

(12) Raucher, S.; Lui, A. S.-T. *J. Am. Chem. Soc.* **1978**, *100*, 4902 and references therein.

(13) It is noteworthy that the ortho ester Claisen rearrangement with 2-(hydroxymethyl)pyridine results in the [3,3]-rearrangement product via ketene acetal, exclusively. See: Costin, C. R.; Morrow, C. J.; Rapoport, H. *J. Org. Chem.* **1976**, *41*, 535.

(14) These [1,3]STR processes seem to proceed in a radical scission–recombination route because the alcohol **22** has been obtained in 16–20% yield



22

whenever the thermolysis is conducted in a nondegassed *o*-dichlorobenzene. ^1H NMR ($CDCl_3$, 100 MHz) δ 1.49 (3 H, s), 3.70 (1 H, s, D_2O exchangeable), 3.83 (3 H, s), 5.24 (1 H, d, J = 14 Hz), 5.44 (1 H, d, J = 14 Hz), 6.83 (1 H, dd, J = 8, 3 Hz), 7.05 (1 H, d, J = 8 Hz), 7.18 (1 H, d, J = 3 Hz); IR ($CHCl_3$) 3530, 1740 cm^{-1}; MS (25 eV), m/e 208 (M^+). Anal. Calcd for $C_{11}H_{12}O_4$: 208.0735. Found: 208.0750.

(15) For thermal [1,3]-sigmatropic rearrangement, see: Lown, J. W.; Akhtar, M. H.; McDaniel, R. S. *J. Org. Chem.* **1974**, *39*, 1998. Padwa, A.; Cohen, L. A. *J. Org. Chem.* **1984**, *49*, 399.

(16) Sigmatropic rearrangement of five-membered heteroaromatics, see: Thomas, A. F.; Ozainne, M. *J. Chem. Soc. C* **1970**, 220. Raucher, S.; Lui, A. S.-T.; Macdonald, J. E. *J. Org. Chem.* **1979**, *44*, 1885. Nemoto, H.; Shitara, E.; Fukumoato, K.; Kametani, T. *Heterocycles* **1985**, *23*, 549 and references therein. A recent example of [1,3]-sigmatropic rearrangement of furfuryloxy enamines: Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1427.

(17) The competitive [3,3]- and [1,3]-sigmatropic rearrangements, see: Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1980**, *45*, 891. Wilson, S. R.; Price, M. F. *J. Org. Chem.* **1984**, *49*, 722.

(18) A 2:1–3:2 ratio of diastereomers was detected by ^1H NMR and ^{13}C NMR spectroscopies.

Enantioselective Synthesis of *anti*-α-Methyl-β-hydroxy Esters through $TiCl_4$-Mediated Aldol Condensation

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While a variety of excellent methods have been developed for the enantioselective synthesis of *syn*-α-methyl-β-hydroxy esters via the aldol reaction,[1] methods for the enantioselective construction of the anti counterparts have been slower in coming[2] and have met with much less success.[3] Here we report a rational solution to this problem, fulfilling the following requirements: (a) enantiomeric excess >90% and high chemical yields; (b) both enantiomers of the chiral inductor are inexpensive, commercially available materials; (c) the chiral inductor can be recycled; (d) the absolute configuration of the reaction products is easily predictable.

As it is well-known that silyl ketene acetals, generated from propionates under kinetic control, react with aldehydes in the presence of a Lewis acid to give mostly anti aldol condensation products,[1,4] we thought to use $TiCl_4$ as a stereochemical template for an anti-selective, asymmetric aldol reaction. By use of the

(1) Heathcock, C. H. "Asymmetric Synthesis"; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Part B, pp 111–212 and references therein.

(2) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1–76 and references therein.

(3) For recent progress in this area, see: (a) Meyers, A. I.; Yamamoto, Y. *Tetrahedron* **1984**, *40*, 2309. (b) Jephcote, V. J.; Pratt, A. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1984**, 800. (c) Masamune, S.; Kaiho, T.; Garvey, D. S. *J. Am. Chem. Soc.* **1982**, *104*, 5521. Boschelli, D.; Ellingboe, J. W.; Masamune, S. *Tetrahedron Lett.* **1984**, 3395. (d) Brown, J. M.; Cutting, I. *J. Chem. Soc., Chem. Commun.* **1985**, 578.

(4) Chan, T. H.; Aida, T.; Lau, P. W. K.; Gorys, V.; Harpp, D. N. *Tetrahedron Lett.* **1979**, 4029. Heathcock, C. H.; Hug, K. T.; Flippin, L. A. *Tetrahedron Lett.* **1984**, 5973.

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