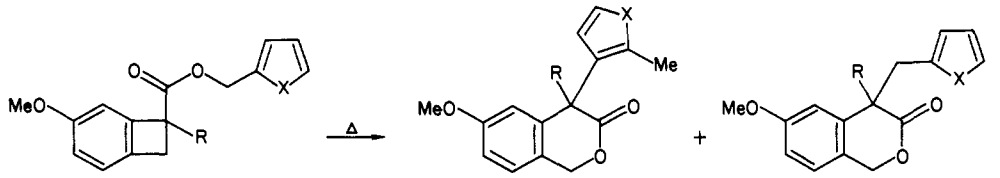
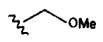
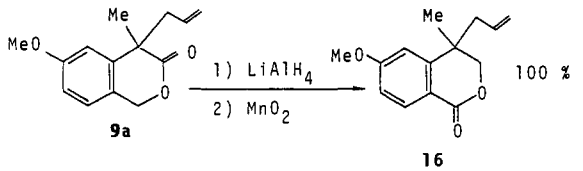
Table III. Competitive Tandem Electrocyclic-Sigmatropic Reaction



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.

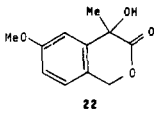
Acknowledgment. We thank Professor D. Seebach, ETH, for valuable discussions on the reaction mechanism.

(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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Table I. Results of the Asymmetric Aldol Reactions Using (1*R*,2*S*)-*N*-Methylephedrine

entry	R-CHO	anti/syn	*anti*-**1**/*anti*-**2**	*syn*-**3**/*syn*-**4**	% yield[c]	methyl ester **5**		methyl ester **6**	
						% yield	% ee	% yield	% ee
1	Ph	85:15[a,b]	34:1[a,b]	4.5:1[a]	80	60	94.0[d,e]	10	64.0[f]
2	n-C_5H_{11}	75:25[a,b]	*g*	*g*	60	66	93.0[d,e]	22	70.0[h]
3	n-C_3H_7	80:20[a,b]	*g*	*g*	88	60	91.0[d,e]	15	52.5[h]
4	(*E*)-CH_3CH=CH	80:20[a,b]	≥25:1[a,b]	*g*	78	52	91.0[d,h]	13	70.0[h]
5	(*E*)-PhCH=CH	85:15[a,b]	≥25:1[a,b]	*g*	60	60	91.0[d,h]	10	24.0[h]

[a] Ratio determined by 200-MHz ^1H NMR spectroscopy. [b] Ratio determined by isolation of the adducts (flash chromatography). [c] Overall yield of silylation and aldol condensation. [d] The methyl ester with 100% ee was easily obtained starting from the isolated major stereoisomer *anti*-**1**, obtained by flash chromatography. [e] The enantiomeric excess was assessed by optical rotation comparison (see ref 3a,3b) and by ^1H NMR spectroscopy in the presence of Eu(hfc)$_3$. [f] The enantiomeric excess was assessed by optical rotation comparison (see: Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127) and by ^1H NMR spectroscopy in the presence of Eu(hfc)$_3$. [g] Not detectable by ^1H NMR spectroscopy. [h] The enantiomeric excess was assessed by ^1H NMR spectroscopy in the presence of Eu(hfc)$_3$.

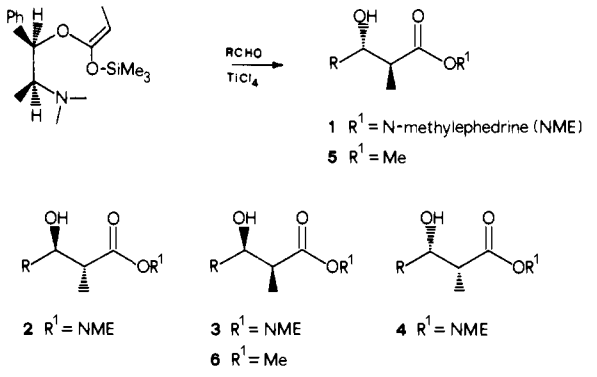

Figure 1. $TiCl_4$-mediated aldol reactions of the *E* silylketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine-*O*-propionate leading to the major stereoisomer *anti*-**1**. Shown are the other isomers *anti*-**2**, *syn*-**3**, *syn*-**4**.

E silylketene acetal derived from (1*R*,2*S*)-*N*-methylephedrine-*O*-propionate, both the aldehyde carbonyl[5] and the ephedrine NMe_2 group are expected to bind to $TiCl_4$, which usually ligates two-electron-donating molecules to form cis-octahedral, six-coordinate complexes.[6] Therefore the conformational freedom of the system is likely to be dramatically reduced, and the C–C bond formation occurs on the six-coordinate metal in a highly stereoselective way.[7]

N-Methylephedrine (1*R*,2*S*) was treated with CH_3CH_2COCl in CH_2Cl_2 to give the *O*-propionate (100%). LDA enolization (THF, −78 °C) and Me_3SiCl trapping (−78 °C) gave the silylketene acetal (95%; *E*/*Z* ≥95:5), which was worked up by evaporation without water quenching. Addition of 1 mol equiv of the silyl ketene acetal in methylene chloride to 1 mol equiv of the $TiCl_4$–aldehyde complex at −78 °C in CH_2Cl_2 gave high overall yields of the aldol condensation products with remarkable stereoselectivity (Figure 1, Table I).[8]

The observed anti/syn ratios (3–5.6:1, Table I) are different from those reported for the related simple alkyl propionates[4] and are markedly dependent on the π-conjugation (more conjugation, higher ratio) and on the steric hindrance (more hindrance, lower ratio) of the aldehyde used.[9] The adducts were treated with NaOH (H_2O–MeOH, room temperature) and then with CH_2N_2 (Et_2O) to give the methyl esters in good yield and optically pure *N*-methylephedrine which could be recycled. The major stereoisomers *anti*-**1** could be easily isolated by flash chromatography and converted to the optically pure methyl esters **5**.

It is worth noting that both the syn and the anti methyl esters **5** and **6** have the same absolute configuration at C-2 (*S*). This shows that, while the aldehyde π-facial selectivity is only moderate, the silylketene acetal π-facial selectivity is very high.

An extention of this methodology to other reactions is under current investigation.

Supplementary Material Available: Detailed experimental procedures for the reactions, analyses, optical rotations, and spectroscopic data (^1H NMR, IR) for the compounds are provided (6 pages). Ordering information is given on any current masthead page.

(5) For general references to the Lewis acid–carbonyl complexation, see: Fratiello, A.; Kubo, R.; Chow, S. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1205. Lienard, B. H. S.; Thomson, A. J. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1400. Olah, G. A.; O'Brien, D. H.; Calin, M. *J. Am. Chem. Soc.* **1967**, *89*, 3582. Brookhart, M.; Levy, G. C.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 1735. Grinvald, A.; Rabinovitz, M. *J. Chem. Soc., Perkin Trans. 2* **1974**, 94. Thil, L.; Riehl, J. J.; Rimmelin, P.; Sommer, J. M. *J. Chem. Soc., Chem. Commun.* **1970**, 591. Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556 and references therein. The crystal structure of the benzaldehyde–BF_3 complex has been recently determined (Reetz, M. T., personal communication).

(6) The crystal structure of a cis-octahedral, six-coordinate titanium complex containing a seven-membered ring chelate structure has been recently reported: Poll, T.; Metter, J. O.; Helmchen, G. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 112.

(7) A detailed analysis of the possible transition states leading to the four diastereoisomers and a complete account of the observed selectivity will be given in a full paper.

(8) The stereochemical outcome of the reaction was found to be relatively independent of the silylketene acetal double-bond geometry. In fact the (*Z*/*E* 65:35) silylketene acetal obtained using $LiN(SiMe_3)_2$ as base instead of LDA gave the following result with benzaldehyde: anti/syn 80:20; *anti*-**1**/*anti*-**2** ≥ 22:1; 65% overall yield. The stereochemical outcome is not even affected by a different mode of addition of the reagents: by treatment of the silylketene acetal first with $TiCl_4$ (30 min, −78 °C) and then with benzaldehyde, the same result as in Table I, entry 1 (yield and selectivity), was obtained.

(9) The anti/syn ratios worsen with aldehyde α-branching. For example: isobutyraldehyde, yield 59%; anti/syn 67:33; *anti*-**1**/*anti*-**2** ≥ 20:1; *syn*-**3**/*syn*-**4** ≥ 8:1.

Synthesis of Branched Ribonucleotides Related to the Mechanism of Splicing of Eukaryotic Messenger RNA

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Since Wallace and Edmonds[1] first discovered a branched structure of RNA from polyadenylated heterogenous nuclear RNAs, considerable attention has been paid to this unique structure in relation to the mechanism of RNA splicing.[2] Very recently, Green[3a] and Sharp[3b] have reported a new type of

(1) Wallace, J. C.; Edmonds, M. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 950.

(2) (a) Weissmann, C. *Nature (London)* **1984**, *311*, 103. (b) Keller, W. *Cell* **1984**, *39*, 432.

(3) (a) Ruskin, B.; Krainer, A. R.; Matiatis, T.; Green, M. R. *Cell* **1984**, *38*, 317. (b) Padgett, R. A.; Konarska, M. M.; Grabowski, P. J.; Hardy, S. F.; Sharp. P. A. *Science (Washington D.C.)* **1984**, *225*, 898. (c) Zeitlin, S.; Efstratiadis, A. *Cell* **1984**, *39*, 589. (d) Rodriquez, J. R.; Pikielny, C. W.; Rosbash, M. *Cell* **1984**, *39*, 603. (e) Domdey, H.; Apostol, B.; Lin, R.-J.; Newman, A.; Brody, E.; Abelson, J. *Cell* **1984**, *39*, 611. (f) Tabak, H. F.; Van der Horst, G.; Osinga, K. A.; Arnberg, A. C. *Cell* **1984**, *39*, 623.

(4) Compound **2** was prepared by the procedure reported by: Markiewicz, W. T. *J. Chem. Res., Synop.* **1979**, 24.

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