Enhanced reactivity and *anti* selectivity in the asymmetric Lewis acid-mediated Mukaiyama aldol reaction of α-alkoxythiolketene acetals with α,β-disubstituted enals: synthesis of the C26–C33 segment of rapamycin

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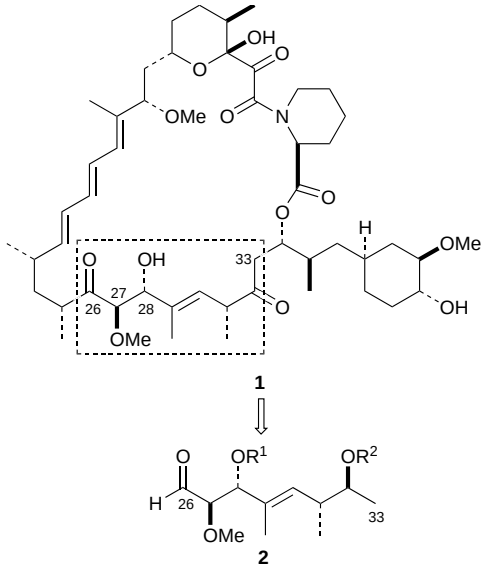
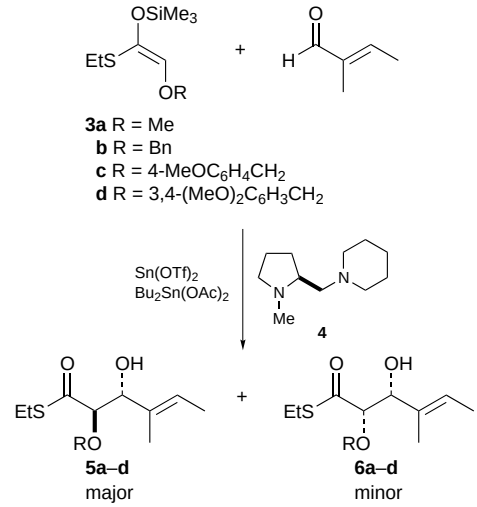
The tin(II)-mediated reaction of α-alkoxythiolketene acetals 3a–d with *trans*-2-methylbut-2-enal and aldehyde 10 was found to give enhanced reactivity and high *anti* selectivity in the glycolate product when an α-benzyloxy substituent was present in 3, a finding which was applied to the synthesis of a segment (C26–C33) of the immunosuppressant rapamycin.

In the course of our studies directed towards a total synthesis of the immunosuppressive agent rapamycin **1**,[1] a subunit was



required which contained functionality suitable for its incorporation as the C26–C33 segment of the macrolide. A difficulty associated with preparing such a fragment resides in controlling relative and absolute configuration of the vicinal *anti* diol moiety at C27–C28. In an attempt to solve this problem in the context of synthesis of a segment **2** required for rapamycin, we were attracted by the chiral Lewis acid-mediated *anti* glycolate aldolization methodology of Mukaiyama[2] and Fukuyama,[3] in which α-alkoxythiolketene acetals were reacted with aldehydes in the presence of tin(II) trifluoromethanesulfonate (triflate) and a proline-derived diamine ligand.[4] We now report that this methodology is readily extended to sterically demanding α,β-disubstituted enals, that both the reactivity and diastereoselectivity of the aldol process are controlled by the ketene acetal α-alkoxy substituent, and that appropriate selection of the *O*-protecting group of the ketene acetal allows differentiation of the adjacent oxygen functions in the aldol product.

Our initial studies were carried out with *trans*-2-methylbut-2-enal and the four α-alkoxythiolketene acetals **3a–d** (Scheme 1). The latter were synthesized from the corresponding thiol esters† by low temperature silylation [lithium tetramethylpiperidine (LTMP), −100 °C, Me_3SiCl] and were obtained predominantly as the (*Z*) isomer in each case. The reaction of ketene



Scheme 1

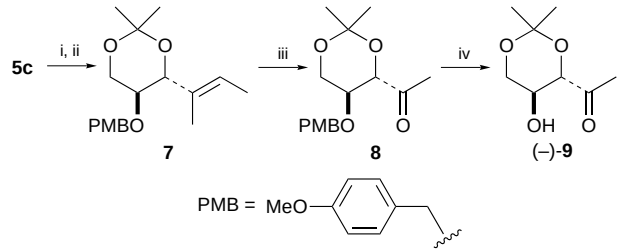
acetals **3a–d** with *trans*-2-methylbut-2-enal in the presence of (*S*)-1-methyl-2-[(1-piperidyl)methyl]pyrrolidine **4** under the conditions specified by Mukaiyama[2] gave aldol adducts **5** and **6** as a mixture of diastereoisomers‡ (Table 1). The *anti* adducts **5a–d** were found to be the major stereoisomers in each case;§ their optical purity was determined by chiral HPLC analysis¶ and by comparison with diastereoisomerically pure racemates synthesized independently. Absolute configuration was assigned in the case of **5c** by correlation with a substance of known stereochemistry (Scheme 2). Thus, reduction of thiol ester **5c** to the corresponding 1,3-diol, followed by acetonide formation, yielded **7** which after ozonolysis gave ketone **8**. Removal of the *p*-methoxybenzyl ether afforded (−)-**9** [$[\alpha]_D^{23}$ −24.8 (*c* 1.0, CH_2Cl_2)] which exhibited spectral data and analytical properties identical to those of its antipode (+)-**9** [$[\alpha]_D^{23}$ +23.6 (*c* 1.0, CH_2Cl_2)‖ prepared from D-glucose.[5]

The results in Table 1 indicate that an increase in both chemical yield *and* diastereoselectivity is observed in the aldol reaction of Scheme 1 when an electron-releasing α-alkoxy

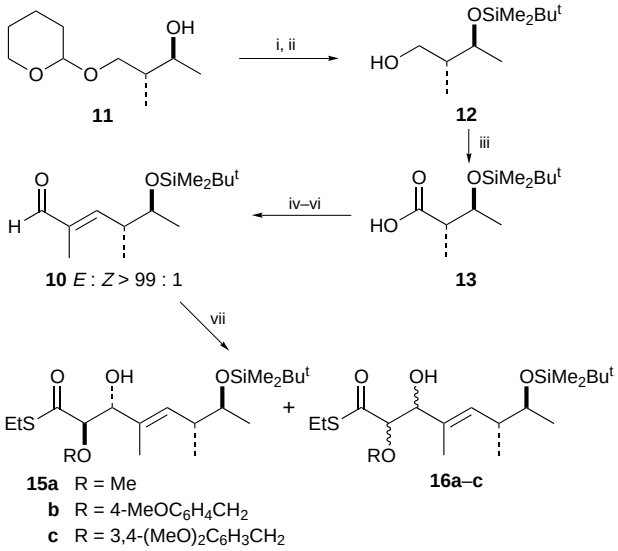
Table 1 Asymmetric Lewis acid-catalysed reaction of *trans*-2-methylbut-2-enal with α-alkoxythiolketene acetals[a]

Ketene acetal (*Z*:*E*)	Aldol products (**5** and **6**) R	Yield (%)[b]	*Anti* (**5**): *syn* (**6**)[c]	Ee of **5** (%)[d]
3a (4:1)	Me	32	70:30	87
3b (12:1)[e]	Bn	82[f]	85:15	93
3c (10:1)	4-$MeOC_6H_4CH_2$	74	90:10	96
3d (6:1)	3,4-$(MeO)_2C_6H_3CH_2$	80	95:5	92

[a] Reactions were carried out in CH_2Cl_2 at −78 °C for 30–36 h except where specified. [b] Isolated yield of **5** + **6**, except where specified. [c] See footnote §. [d] See footnote ¶. [e] Experiment carried out at −50 °C. [f] Isolated yield of **5**.



Scheme 2 *Reagents and conditions*: i, $LiAlH_4$, THF, 0 °C → room temp., 3 h; ii, $Me_2C(OMe)_2$, TsOH, room temp., 2 h, 80%; iii, O_3, MeOH–pyridine (cat), −78 °C, 4 min, then Me_2S, 95%; iv, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ): CH_2Cl_2–H_2O, 48%



Scheme 3 *Reagents and conditions*: i, Bu^tMe_2SiCl, imidazole, CH_2Cl_2, room temp., 12 h; ii, $MgBr_2{\cdot}OEt_2$ (excess), Et_2O, 4 h, 93%; iii, Pr_4NRuO_4 (cat), 4-methylmorpholine *N*-oxide, CH_2Cl_2, room temp., 15 min, *ca*. 100%; iv, LDA, $Bu^tN{=}CHCH(Me)SiMe_3$ **14**, THF, −78 °C; v, $(HO_2C)_2$, H_2O; vi, I_2 (cat), Bu^tNH_2, hexane, 50 °C, 12 h, 62% from **13**; vii, **4**, $Sn(OTf)_2$, $Bu_2Sn(OAc)_2$, **3a**,**c**,**d**, CH_2Cl_2, −78 °C, 30–36 h

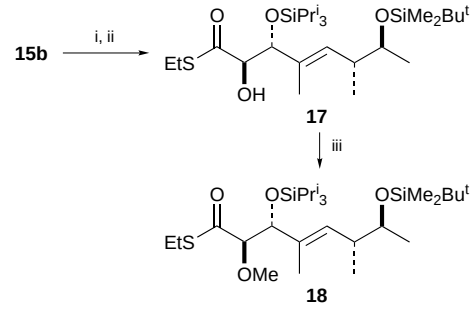
substituent such as 4-methoxybenzyl (PMB) or 3,4-dimethoxybenzyl (DMB) is present in the thiolketene acetal. Best results were obtained with DMB, whereas an α-methoxy substituent resulted in low diastereoselectivity and poor yield.

With this information in hand, our efforts focused upon α,β-unsaturated aldehyde **10** needed for synthesis of subunit **2**. Alcohol **11**, obtained from methyl (*R*)-3-hydroxy-2-methylpropionate,[6] was transformed to **12**[7] which was oxidized to aldehyde **13** with perruthenate.[8] Conversion of this labile substance to α,β-unsaturated aldehyde **10** was accomplished by the procedure of Corey *et al*.[9] in which condensation of **13** with the α-lithio derivative of imine **14** was followed by mild, acid-catalysed Peterson olefination. The initial *ca*. 2 : 1 mixture of (*E*) and (*Z*) isomers of enals was smoothly equilibrated to a > 99 : 1 ratio favouring (*E*) isomer **10** upon exposure to a catalytic quantity of iodine in warm hexane containing a trace (6 mol%) of *tert*-butylamine (Scheme 3).

Table 2 Asymmetric Lewis acid-catalysed aldol reaction of **10** with α-alkoxythiolketene acetals

Ketene acetal	Aldol Products (**15** and **16**) R	Yield (%)	*Anti* (**15**) : *syn*(**16**)[a]
3a	Me	7	75 : 25
3c	4-$MeOC_6H_4CH_2$	54	90 : 10
3d	3,4-$(MeO)_2C_6H_3CH_2$	80	92 : 8

[a] See footnote §.



Scheme 4 *Reagents and conditions*: i, Pr^i_3SiOTf, 2,6-lutidine, CH_2Cl_2, −40 → °C; ii, DDQ, CH_2Cl_2–H_2O, room temp., 1.5 h, 85% from **15b**; iii, CH_2N_2, $BF_3{\cdot}OEt_2$ (1 equiv.), CH_2Cl_2, 94%

The reaction of **10** with α-alkoxythiolketene acetals **3a**,**c**,**d** under the conditions employed with *trans*-2-methylout-2-enal yielded *anti* aldol products **15a**–**c** as the major diastereoisomers (Table 2). Again, PMB- and DMB-substituted ketene acetals **3c** and **3d** showed superior stereoselectivity, whereas α-methoxy derivative **3a** was virtually unreactive with **10**. Protection of **15b** as its triisopropylsilyl ether, followed by oxidative cleavage of the PMB ether,[10] gave **17** (Scheme 4), and treatment of the liberated alcohol with CH_2N_2 in CH_2Cl_2 containing $BF_3{\cdot}OEt_2$ furnished methyl ether **18**. This material now stands ready in conveniently protected form for connection at each terminus to other subunits required for the synthesis of **1**.

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Footnotes and References

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† Thiol esters were prepared either by reaction of the corresponding acyl chloride with EtSH or from the corresponding benzylglycolic acid by treatment with DCC, catalytic DMAP and EtSH (ref. 11). 4-Methoxybenzylglycolic acid and 3,4-dimethoxybenzylglycolic acid were obtained in 91 and 87% yield, respectively, by ether synthesis from chloroacetic acid and the corresponding sodium benzylates (NaH, toluene, reflux).

‡ In the case of **3b**, adducts were separated by flash chromatography.

§ Diastereoselectivities were determined by ^1H NMR analysis of crude reaction mixtures after workup.

¶ Chiral HPLC column: DAICEL ChiralPak AD, 350 × 4 mm.

‖ This value is in conflict with that reported by David *et al*.[5] for (+)-**9** [$[\alpha]_D^{20}$ +40.5 (*c* 7, CH_2Cl_2)], which is shown to be in error by this work.

1 J. D. White and S. C. Jeffrey, *J. Org. Chem.*, 1996, **61**, 2600.
2 T. Mukaiyama, *Aldrichim. Acta*, 1996, **29**, 59; T. Mukaiyama, I. Shiina, K. Sakata, T. Emura, K. Seto and M. Saitoh, *Chem. Lett.*, 1995, 179; T. Mukaiyama, I. Shiina, H. Uchiro and S. Kobayashi, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1708.
3 Y. Kanda and T. Fukuyama, *J. Am. Chem. Soc.*, 1993, **115**, 8451.
4 T. Mukaiyama, N. Iwasawa, R. W. Stevens and T. Haga, *Tetrahedron*, 1984, **40**, 1381.
5 S. David, B. Estramereix, J.-C. Fischer and M. Thérisod, *J. Chem. Soc., Perkin Trans. 1*, 1982, 2131.
6 R. Baker, R. H. Boyes, D. M. P. Broom, M. J. O'Mahony and C. J. Swain, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1613.
7 K. Mori and M. Itou, *Liebigs Ann. Chem.*, 1992, 87.
8 L. A. Paquette, C. F. Sturino, X. Wang, J. C. Prodger and D. Koh, *J. Am. Chem. Soc.*, 1996, **118**, 5620.
9 E. J. Corey, D. Enders and M. G. Bock, *Tetrahedron Lett.*, 1976, 7.
10 K. Horita, T. Yoshioka, T. Tanaka, Y. Oikawa and O. Yonemitsu, *Tetrahedron*, 1986, **42**, 3021.
11 B. Neises and W. Steglich, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 522.

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