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A SHORT ASYMMETRIC SYNTHESIS OF A C_{19}-C_{27} SEGMENT OF RIFAMYCIN S. KINETIC RESOLUTION IN THE ALDOL REACTIONS OF ETHYLKETONES USING CHIRAL BORON REAGENTS

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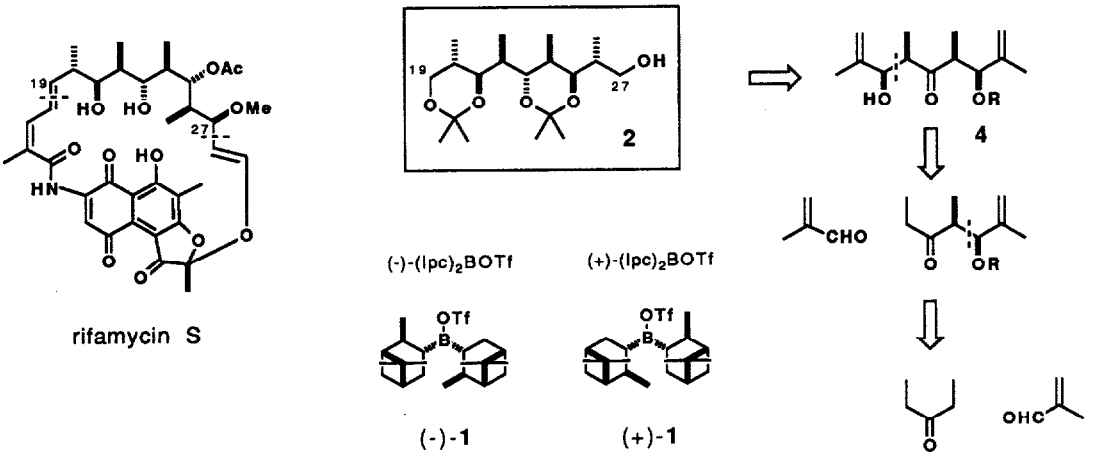
Summary: The chiral reagents (+)- and (-)-$(Ipc)_2BOTf$ are used to control the aldol addition reactions of ethylketone **3** with methacrolein. Under suitable conditions, racemic **3** can be converted into the SS aldol adduct (+)-**4** in ≥95% ee with >95% diastereoselectivity. Resolved starting ketone (+)-**3** can be recovered in ≥95% ee. Adduct (+)-**4** was converted into the rifamycin S segment (-)-**2** *via* stereoselective ketone reduction and hydroboration.

Rifamycin S, an important member of the ansamycin class of macrolide antibiotics, has been the subject of intense synthetic interest.[1] Following on from the landmark total synthesis reported by Kishi and coworkers in 1980,[2a,b] several syntheses of the polypropionate ansa bridge have been completed, which feature different strategies for controlling this sequence of eight contiguous stereogenic centres.[1,2c,3] We now report a short asymmetric synthesis of **2**, a C_{19}-C_{27} segment of rifamycin S used in the Kishi synthesis, based on ethylketone aldol reactions mediated by the α-pinene derived boron reagents (-)-**1** and (+)-**1**.[4] As part of this synthesis, we also describe the novel use of these chiral reagents for the kinetic resolution[5] of racemic ethylketones.

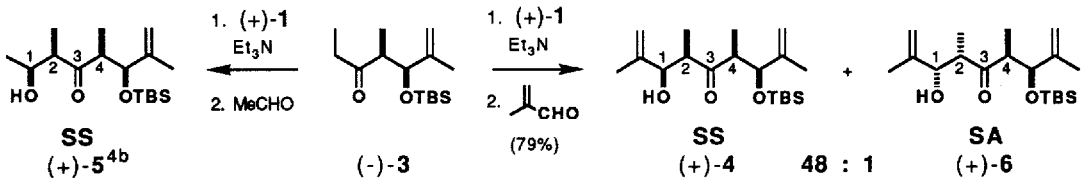
Scheme 1



Our retrosynthetic analysis for **2**, as shown in **Scheme 1**, requires control of the double aldol addition of diethylketone with methacrolein to give the adduct **4** (R=TBS) in enantiomerically enriched form. We have already described an enantioselective synthesis of the ketone **5** (**Scheme 2**) using the reagents (-)-**1** and (+)-**1** to control the first[4a] and second[4b] aldol reaction with methacrolein and acetaldehyde, respectively. This chemistry is easily adapted to the synthesis of **4** by using methacrolein twice.

Enolisation of (-)-**3** (90% ee) by (+)-**1** (Et_3N, CH_2Cl_2, 0°C, 5 h), followed by aldol addition to methacrolein (0°C, 12 h; H_2O_2), gave the **SS** (*i.e.* 1,2-*syn*-2,4-*syn*) isomer (+)-**4**[6] (93% ee)[7] with 97% diastereoselectivity in 79% yield. HPLC analysis of the crude aldol mixture showed the formation of 2% **SA** (1,2-*syn*-2,4-*anti*) and *ca* 1% of the 1,2-*anti* isomers. Here the π-face selectivity of the Z-enolate is enhanced by the matched influence of the chiral ligands on boron. If the mismatched combination was used with (-)-**1**, the diastereoselectivity towards (+)-**4** was reduced to 64% with a significant amount (29%) of the **SA** isomer (+)-**6** now obtained from attack on the opposite enolate π-face.

Scheme 2



Kinetic resolution[5] should be possible in the aldol reaction of the *racemic* ethylketone **3** using (+)-**1** (**Scheme 3**), if the matched enolate system **7**, which reacts with high π-face selectivity (*ca* 50:1 **SS**:**SA**), was to react significantly *faster* with the aldehyde than the mismatched enolate **8**, which reacts with low π-face selectivity (*ca* 2:1 **SS**:**SA**). At *ca* 50% conversion, this should then selectively give the desired aldol product (+)-**4** *via* the fast-reacting enolate **7**. At the same time, recovered unreacted ketone should be enriched in (+)-**3** from the slow-reacting enolate **8**.

Scheme 3

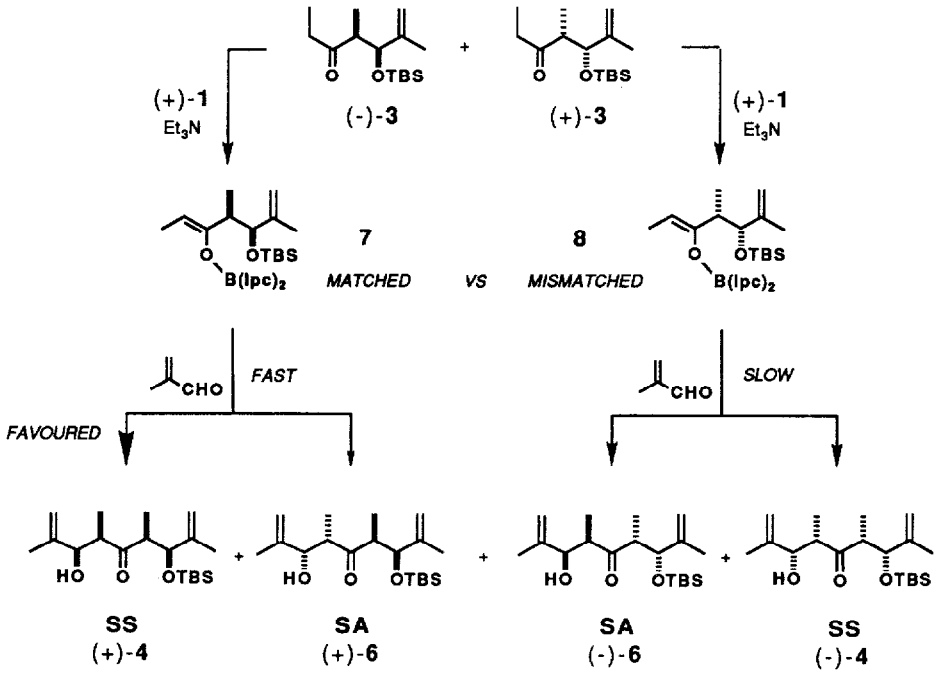
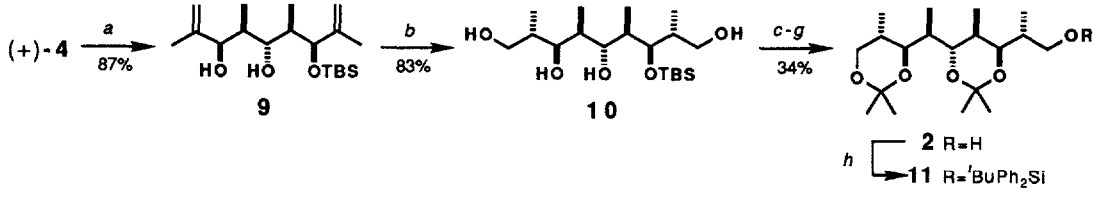


Table Kinetic resolution of ketone (±)-**3** in aldol reaction with methacrolein using boron triflates (-)-**1** and (+)-**1** with Et_3N in CH_2Cl_2. Enolisation (0°C, 4 h) and oxidative workup (H_2O_2, pH7 buffer/MeOH) conditions are standard.

				product composition (SS=**4** and SA=**6**)[b]			recovered **3**[f]	
entry	reagent (equiv.)[a]	aldehyde equiv.	aldol conditions time/temp (°C)	% yield **4**	% ee **4**[c] ($[\alpha]_D$)[d]	SS:SA[e]	% recovery	% ee**3**[g] (rot.[h])
1	(-)-**1** (1.3)	0.4	14 h/0; 2.5 h/20	24	91	28:1	45	45 (-)
2	(-)-**1** (1.5)	0.5	19 h/0; 2 h/20	34	89	29:1	40	70 (-)
3	(-)-**1** (1.5)	1.5	2 h/0; 18 h/20	41	55 (-33.7)	27:1	20	93 (-)
4	(+)-**1** (2.0)	0.5	17 h/0; 3.5 h/20	36	≥95 (+62.1)	45:1[i]	51	40 (+)
5	(+)-**1** (1.5)	1.5	2 h/0; 18 h/20	48	55 (+36.0)	23:1	25	≥95 (+)

[a] As a *ca* 1M solution in hexane. [b] Isolated aldol adducts after chromatography. [c] Determined from analysis of Mosher ester. [d] Measured in $CHCl_3$. [e] Ratio of **4**:**6** by HPLC. [f] Recovered **3** after chromatography. [g] Determined from analysis of Mosher ester and/or chiral shift ^{1}H-NMR using Eu(hfc)$_3$ on free β-hydroxyketone after TBS deprotection. [h] Sign of rotation of recovered **3** in $CHCl_3$. [i] 4% of 1,2-*anti* isomers were obtained.

Using the reagents (-)-**1** (entries 1-3) and (+)-**1** (entries 4-5), our results for the aldol reaction of (±)-**3**[8] with methacrolein are shown in the **Table**. The conversion was controlled by varying the amount of reagent and aldehyde used, together with the aldol reaction temperature. To avoid any complication from kinetic resolution in the enolisation step itself,[9] we employed excess reagent (1.3-2.0 equiv.) to ensure complete conversion to the enolates. In one run using 1.3 equiv. of (-)-**1** for enolisation and 0.4 equiv. of aldehyde (entry 1), the SS isomer (-)-**4** was obtained in 91% ee with 95% diastereoselectivity and the recovered ketone (-)-**3** in 45% ee.[6] Use of slightly more reagent and aldehyde gave increased conversion (entry 2), producing (-)-**4** in 89% ee and providing recovered (-)-**3** in 70% ee. Increasing the conversion further (entry 3) led to recovered ketone (-)-**3** in 93% ee. Carrying out these same reactions with the enantiomeric reagent (+)-**1** led to production of the desired adduct (+)-**4** in ≥95% ee with high diastereoselectivity, SS:SA =45:1 (entry 4). Increased conversion gave recovered (+)-**3** in ≥95% ee (entry 5), thus demonstrating essentially complete kinetic resolution of the ketone.



Scheme 4: (*a*) $Me_4N.HB(OAc)_3$ (10 equiv.), 1:1 AcOH/MeCN, 20°C, 20 h; (*b*) 9-BBN (6 equiv.), THF, 20°C, 3 h; NaOOH; (*c*) $(MeO)_2CMe_2$, CH_2Cl_2, PPTS, 20°C, 2 h; (*d*) ^{t}BuCOCl, pyridine, CH_2Cl_2, 0 → 20°C, 3 h; (*e*) TBAF, THF, 20°C, 1 h; (*f*) $(MeO)_2CMe_2$, CH_2Cl_2, PPTS, 20°C, 3 h; (*g*) $LiAlH_4$, Et_2O, 20°C, 2 h; (*h*) ^{t}BuPh$_2$SiCl, DMAP, imidazole, CH_2Cl_2, 20°C, 0.5 h.

Final conversion of (+)-**4** to the C_{19}-C_{27} rifamycin S segment **2** (**Scheme 4**) required stereoselective ketone reduction and alkene hydration. This sequence of steps was carried out on material of 91% ee. The reduction, **4** → **9**, was achieved with 97% diastereoselectivity (HPLC analysis) in 87% yield by using $Me_4N.HB(OAc)_3$ (1:1

MeCN/AcOH, 20°C).[10] Hydroboration of the diol **9**[11] using excess 9-BBN (THF, 20°C) then gave predominantly (80% diastereoselectivity) one tetraol isomer **10** with stereochemistry as predicted by the work of Still and Barrish.[12] This sequence of seven stereogenic centres, therefore, can be simply and quickly set up in five steps from diethylketone with 72% stereoselectivity. Straightforward protecting group manipulation (five steps) was finally used to convert **10** into (-)-**2**, $[\alpha]_D^{20}$= -6.3°(*c* 2.1, $CHCl_3$; 91% ee),[11] which had ^{1}H-NMR and specific rotation data in agreement with those previously reported by Kishi and coworkers.[2c] In addition, the derived *tert*-butyldiphenylsilyl ether **11** was found to have spectroscopic data in agreement with Kishi[2c] and Ziegler *et al*,[3a] thus confirming all of our stereochemical assignments.

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(5) For some recent examples of chemical kinetic resolutions, see: (a) Kitamura, M.; Kasahara, I.; Manabe, K.; Noyori, R.; Takaya, H. *J. Org. Chem.* **1988**, *53*, 708; (b) Brown, J. M.; James, A. P.; Prior, L. M. *Tetrahedron Lett.* **1987**, *28*, 2179; (c) Gennari, C.; Colombo, L.; Bertolini, G.; Schimperna, G. *J. Org. Chem.* **1987**, *52*, 2754; (d) Hayashi, T.; Yamamoto, A.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1986**, 1090; (e) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(6) All new compounds gave spectroscopic data in agreement with the assigned structures. The enantiomeric purity of the SS adduct **4** was determined by ^{1}H-NMR analysis of its (-)-MTPA ester. The enantiomeric purity of the recovered unreacted ketone **3** was determined, after TBS deprotection (5% HF, MeCN, 20°C, 2 h) to give the free β-hydroxy ketone, by chiral shift ^{1}H-NMR studies using Eu(hfc)$_3$ as well as by analysis of its (-)-MTPA ester.

(7) This aldol reaction is accompanied by an upgrading of the enantiomeric purity of the major aldol isomer, *cf* ref 2b. The reaction has also been performed with (-)-**3** of 80% ee, which gave the SS isomer (+)-**4**, $[\alpha]_D^{20}$= +55.6°(*c* 1.8, $CHCl_3$) in 91% ee and 83% yield.

(8) The racemic *syn* isomer (±)-**3** was prepared in 66% overall yield and 98% diastereoselectivity from diethylketone by the sequence (i) 9-BBNOTf, ^{i}Pr$_2$NEt, CH_2Cl_2, -78°C, 2 h; methacrolein, -78→0°C, 3 h; H_2O_2; (ii) TBSOTf, lutidine, CH_2Cl_2, -78°C, 0.5 h. The small amount of *anti* isomer in **3** was removed by flash chromatography.

(9) We checked to see if there was any significant level of kinetic resolution in the enolisation step by using 0.5 equiv. of reagent (-)-**1** and 1 equiv. of methacrolein. In this case, both the recovered ketone **3** and the SS aldol adduct **4** were obtained in <30% ee suggesting that the effect was small.

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(11) Diol **9**, m.p. 96-97°C, could be obtained in enantiomerically pure form, $[\alpha]_D^{20}$= +0.8°(*c* 3.1, $CHCl_3$), by recrystallisation from hexane. In practice, the remaining steps were carried out on material of 91% ee.

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