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Toward a Practical Synthesis of Acutiphycin. Highly Stereoselective Synthesis of C10-*epi* Seco Acid Derivative via Reaction Paths Shortened by Using a Series of Chiral Oxazaborolidinone-Promoted Aldol Reactions[1]

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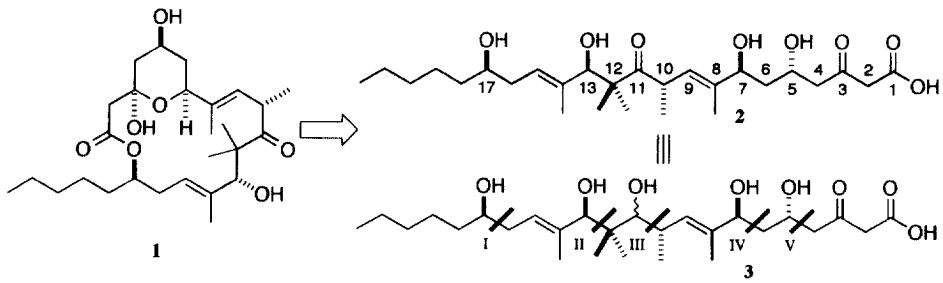
Abstract: A straightforward asymmetric synthesis of the C10-*epi* seco acid derivative of antineoplastic macrolide Acutiphycin was achieved by applying the strategy of the chiral oxazaborolidinone-promoted aldol reaction. By repeated utilization of this highly enantioselective aldol reaction, reaction paths toward the complex acyclic compound under promoter control were substantially shortened.

Modern organic synthesis requires us to deal with selectivity more severely for ecological and environmental reasons. With our continuous studies on the chiral oxazaborolidinone-promoted asymmetric aldol reaction[2] we are aiming to achieve substantial shortening of paths toward complex targets by repeated aldol reactions. The methodology is based on promoter control where an effective acyclic stereoselection is simply achieved if the highly enantioselective asymmetric reaction takes place depending on only the stereochemistry of the promoter.[3] Thus, enantiomerically pure diastereomers can be provided by repeating the asymmetric aldol reactions con-

Scheme 1



trolled by the stereochemistry of the promoter applied.[4] According to this principle, we undertook a straightforward asymmetric synthesis of a macrolide Acutiphycin **1** which proved to show citotoxicity against KB and NIH/3T3 cells and significant antineoplastic activity *in vivo* against Lewis lung carcinoma. The structure elucidation of

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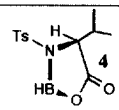
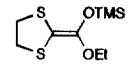
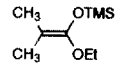
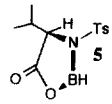
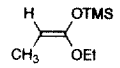
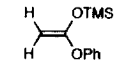
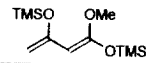
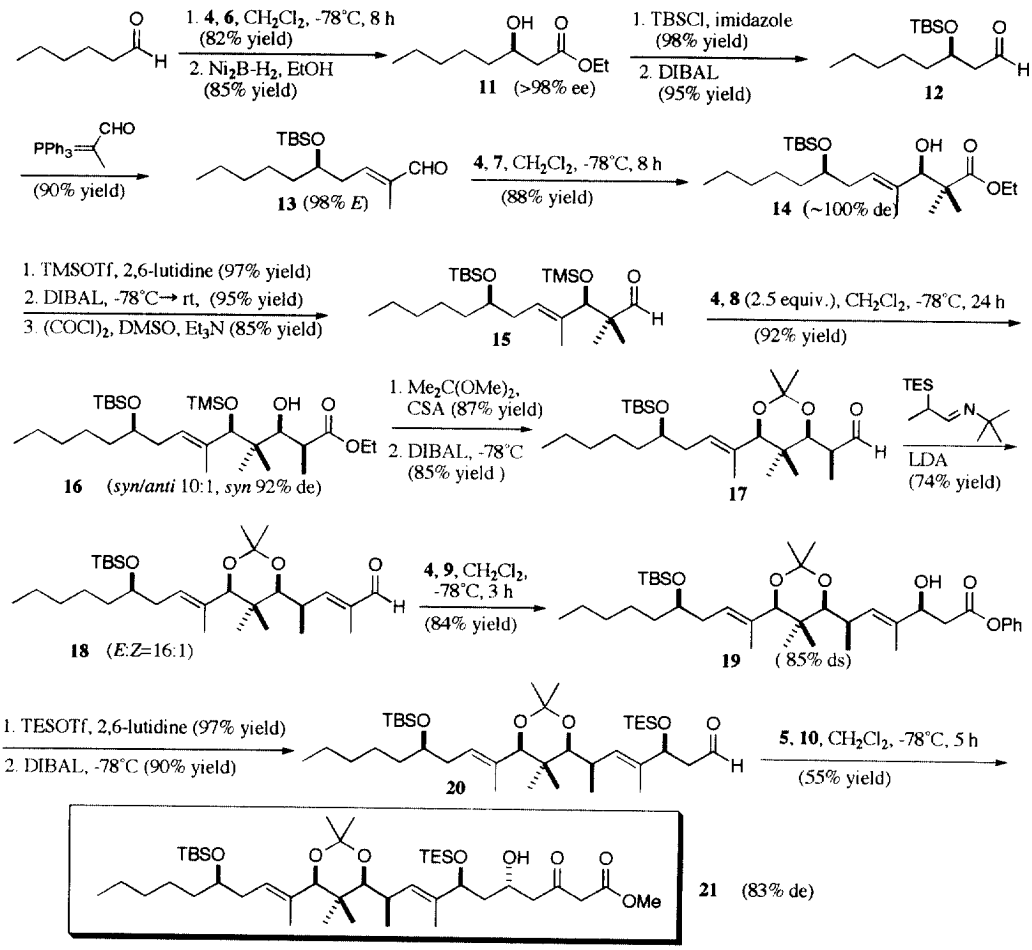
Table 1. A series of five chiral oxazoborolidinone-promoted aldol reactions at the carbon-carbon bonds indicated with slant lines for target molecule **3** in Scheme I

Aldol Reaction	Catalyst (Promoter) Complex	Silyl Nucleophile
I	 **4**	 **6**
II	**4**	 **7**
III	**4** or  **5**	 **8**
IV	**4**	 **9**
V	**5**	 **10**

Scheme II[7]



1 was done by Moore in 1984 [5] and the first total synthesis was elegantly realized with a classical strategy by Smith in 1995.[6]

Our strategy was to construct linearly seco acid **2** by using a series of five aldol reactions at the carbon-carbon bond indicated with slant lines in **3**. The key aldol reactions for the very simple and straightforward synthesis of the seco acid derivative of Acutiphycin are listed with necessary reagents in the presence of a stoichiometric amount of the promoters[8] in Table 1. The first aldol **11** is readily available with >98% ee by adoption of the established enantioselective acetate aldol synthesis[9] using dithiolane silyl ketene acetal **6** in the presence of a stoichiometric amount of **4**, followed by desulfurization with nickel boride under hydrogen atmosphere. Protection and reduction of **11** almost quantitatively gave the corresponding aldehyde **12**. We chose α-formylethylidenetriphenylphosphorane to serve as a versatile Wittig reagent for construction of the *E* isomer.[10] As expected, *E*-olefinic aldehyde **13** was obtained with 98% selectivity. The second aldol reaction of **13** with **7** allowed appropriate preparation of **14** with ~100% de under the standard reaction conditions (CH_2Cl_2, -78°C, 8h).[2] The almost complete level of diastereoselectivity in the addition is attributed to promoter control in which the creation of the new stereogenic center is affected only by the stereochemistry of the promoter **4**.[2] Protection and DIBAL reduction of **14**, followed by Swern oxidation gave a highly hindered aldehyde **15**. The chiral oxazaborolidinone-promoted asymmetric aldol reaction of such highly hindered aldehydes having a quaternary carbon at the α-position has shown a limitation on promoter control along with the enhanced selectivity, as reported from the same laboratory.[1] Thus, the third aldol reaction of **15** with **8** in the presence of **4** resulted in the preferential formation of **16** with 92% de on *syn* isomers (*syn*/*anti*=10 : 1).[11] A large excess of the silyl nucleophile and prolonged reaction time (24 h) were necessary to secure a good yield (92% yield). Unfortunately, the stereochemistry at C 2 of **16** was opposite to that expected in the original target **3**.[12] When the third aldol reaction was carried out in the presence of **5**, **16** was obtained in low yield (54%) along with lower selectivities (60% de, *syn*/*anti*: 4.5 : 1). Protection and reduction of **16** gave an acetonide aldehyde in good yield. The second aldehyde homologation was achieved by using an α-silyl imino reagent (α-triethylsilyl *t*-butylimine of propionaldehyde)[13] to give an olefinic aldehyde **18** with high *E* selectivity. The fourth aldol reaction of **18** with **9** was carried out with considerably high *si*-facial selectivity in the presence of **4**. The somewhat lower level of the selectivity is ascribable not to insufficient catalyst control but to the inherent property of the reaction with α-unsubstituted silyl nucleophile **9**.[2] After protection and reduction, the fifth aldol reaction of **20** with disilyl nucleophile **10** in the presence of **5** permitted a straightforward synthesis of the C 10-*epi* seco acid derivative **21** of Acutiphycin with 83% de.

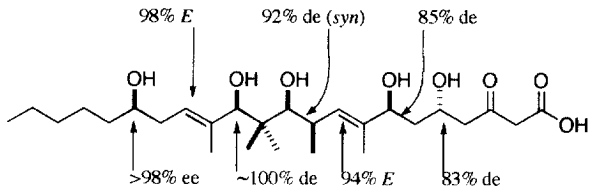


Figure 1. Each selectivity found in the reaction sequence

In summary, we have accomplished a very short, highly enantio- and diastereoselective synthesis of **21** via shortened reaction paths by only repeating the same aldol reaction at the level required for practical applications, although the reverse of the expected stereochemistry in the third aldol reaction was observed. Each selectivity found in the reaction sequence including the olefination processes is listed in Figure 1.

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7. Compound **14**: $[\alpha]^{24}_{D}$ +12 (c 1.0, $CHCl_3$). IR (neat): 3410, 1734cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.04 (s, 3H), 0.05 (s, 3H), 0.88 (s, 9H), 0.87 (t, 3H, J = 7.07), 1.12 (s, 3H), 1.22 (s, 3H) 1.19 - 1.40 (m, 8H), 1.28 (t, 3H, J = 7.07),1.59 (s, 3H), 2.18 (m, 2H), 3.22 (d, 1H, J = 6.09), 3.69 (quin, 1H, J = 6.35), 4.05 (d, 1H, J = 6.09), 4.17 (dq, 2H, J=1.22, 7.07), 5.40 (t, 1H, J = 7.07). ^{13}C NMR ($CHCl_3$, 100 MHz): δ (ppm) -4.5, -4.3, 13.0, 14.0, 14.1, 18.1, 20.9, 22.6, 24.2, 25.0, 31.5, 31.9, 35.6, 36.7, 46.2, 60.8, 71.9, 83.1, 126.2, 135.3, 178.0.
   Compound **16**: $[\alpha]^{24}_{D}$ +22 (c 0.60, $CHCl_3$). IR (neat): 3485, 1712 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.05 (s, 3H), 0.06 (s, 3H), 0.10 (s, 9H), 0.70 (s, 3H), 0.89 (s, 9H), 0.88 (t, 3H, J = 7.07), 0.92 (s, 3H), 1.23 (d, 3H, J = 7.07), 1.25 (t, 3H, J = 7.07), 1.22 - 1.41 (m, 8H), 1.59 (s, 3H), 2.18 (br. t, 2H, J = 6.83), 2.65 (dq, 1H, J = 6.59, 7.07), 3.67 - 3.73 (m, 1H), 3.71 (d, 1H, J = 1.71), 3.93 (dd, 1H, J = 1.71, 6.59), 3.99 (s, 1H), 4.12 (m, 2H), 5.38 (t, 1H, J = 6.83). ^{13}C NMR ($CHCl_3$, 100 MHz): δ (ppm) -4.5, -4.3, 0.0, 13.8, 14.1, 14.2, 16.9, 18.12, 21.51, 22.7, 25.2, 26.0, 32.0, 35.6, 36.7, 41.7, 43.0, 60.3, 71.8, 77.7, 87.4, 126.4, 136.35, 176.8.
   Compound **19**: $[\alpha]^{24}_{D}$ +5 (c 0.80, $CHCl_3$). IR (neat): 3439, 1759, 1595 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.03 (s, 3H), 0.04 (s, 3H), 0.72 (s, 3H), 0.87 (s, 9H), 0.76-0.80 (t, 3H, J=7.00), 0.88 (s, 3H), 0.89 (d, 3H, J = 6.83), 1.19-1.42 (m, 8H), 1.40, (s, 3H), 1.42, (s, 3H), 1.64, (s, 3H), 1.74 (s, 3H), 2.19 (br. t, 2H, J = 6.35), 2.59 (bs, 1H), 2.61-2.65 (m, 1H), 2.68 (dd, 1H, J=3.65, 12.44), 2.80 (dd, 1H, J=6.83, 9.27), 3.29 (d, 1H, J=7.07), 3.66 (quin, 1H, J=5.61), 3.89 (s, 1H), 4.52 (br.d, 1H, J=8.78), 5.35 (t, 1H. J=7.07), 5.46 (d, 1H, J=10.0), 7.08-7.39 (m, 5H). ^{13}C NMR ($CHCl_3$, 100 MHz): δ (ppm) -4.3, -4.5, 0.00, 11.8, 14.0, 14.9, 15.3, 17.8, 18.0, 19.2, 22.6, 25.0, 25.8, 30.0, 31.9, 33.5, 35.7, 36.8, 38.1, 40.0, 72.0, 73.3, 81.2, 83.9, 98.2, 121.4, 125.9, 126.9, 129.4, 131.5, 132.4, 133.2, 150.4, 170.9.
   Compound **21**: $[\alpha]^{24}_{D}$ +17 (c 0.30, $CHCl_3$). IR (neat): 3503, 1747, 1700, 1653 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400MHz): δ (ppm) 0.03 (s, 3H), 0.04 (s, 3H), 0.56 (q, 6H, J=7.80), 0.70 (s, 3H), 0.87 (s, 3H), 0.88 (s, 9H), 0.89 (s, 3H), 0.94 (t, 9H, J=7.80), 0.96 (d, 3H, J = 6.34), 1.20-1.40(m, 8H), 1.25-1.35 (m, 2H), 1.41, (s, 3H), 1.43, (s, 3H), 1.58, (s, 3H), 1.64 (s, 3H), 2.20 (br. t, 2H, J = 6.34), 2.58-2.64 (m, 1H), 2.66 (d, 2H, J=6.09), 3.26 (d, 1H, J=2.92), 3.32 (d, H, J=7.07), 3.48 (s, 2H), 3.69 (t, 1H, J=5.61), 3.73 (s, 3H), 3.89 (s, 1H), 4.23-4.31 (m, 2H), 5.33 (d, 1H, J=10.0), 5.36 (t, 1H. J=7.07). ^{13}C NMR ($CHCl_3$, 100 MHz): δ (ppm) -4.5, -4.3, 6.7, 6.8, 11.7, 14.0, 14.9, 15.3, 17.4, 18.0, 19.2, 22.5, 22.6, 25.0, 25.9, 30.0, 31.9, 33.4, 35.7, 36.8, 38.1, 41.3, 49.5, 50.1, 52.3, 64.5, 72.0, 75.2, 81.1, 83.9, 98.1, 126.8, 131.1, 133.0, 133.3, 167.3, 202.8.
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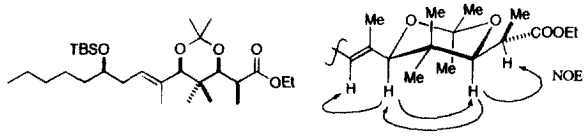

11. The relative stereochemistry of **16** was confirmed by NOE experiments of it's acetonide derivative.
12. For the total synthesis of **1**, the stereochemistry at C10 of **21** might be requested to be epimerized during the coming processes.
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