Double Stereodifferentiating Aldol Reactions Based on Chiral Ketones Derived from Lactic Acid: Synthesis of C1–C6 Fragment of Erythronolides

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Dedicated to the memory of recently deceased Professor Satoru Masamune.

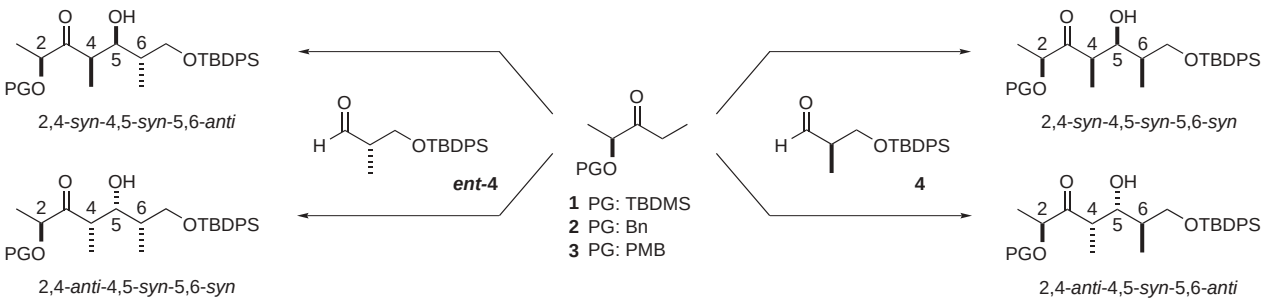
Abstract: Highly stereoselective titanium-mediated aldol additions of ethyl ketones derived from lactic acid to α-methyl-β-OTBDPS chiral aldehydes are documented. One of these double stereodifferentiating processes represents the key step of a straightforward and efficient synthetic approach to the C1–C6 fragment of erythronolides.

Key words: aldol reactions, chiral ketones, erythronolides, stereoselective synthesis, titanium

Pioneering studies by Masamune and Heathcock revealed the synthetic potentiality of α-hydroxy ketones for the stereoselective construction of carbon–carbon bonds through aldol type reactions.[1] They paved the way for the development of a plethora of asymmetric methodologies, and, particularly, inspired our endeavors to devise new stereoselective titanium-mediated aldol transformations based on chiral ketones derived from lactic acid.[2,3] Accumulated evidence so far points out that there are three identifiable stereochemical determinants that influence the reaction diastereoselectivity: (i) the hydroxyl protecting group, (ii) the titanium Lewis acid used in the enolization step, and (iii) the addition of a supplementary Lewis acid to the reaction mixture.[3] Furthermore, conventional wisdom states that chirality on the aldehyde must also play an important role.[4–6] Therefore, we decided to evaluate double stereodifferentiating titanium-mediated aldol reaction between ketones **1–3** and chiral aldehydes **4** and ***ent*-4** (see Scheme 1), aiming to discover simple and highly stereoselective processes useful for the synthesis of polypropionate-like natural products.

Given that the above-mentioned titanium-mediated aldol methodologies[3] only afford *syn* relationships, four stereochemistries represented in Scheme 1 were expected to predominate.

Chiral ketones, **1–3**, and aldehydes, **4** and ***ent*-4**, were prepared in enantiomerically pure form by well-known procedures.[7,8] Aldol reactions were then carried out according to the protocols previously reported.[3] The results summarized in Scheme 2 show that most reactions are highly stereoselective irrespective of the configuration of the aldehyde (compare eq 1 and 2, 5 and 6, and 7 and 8 in Scheme 2), which confirms the high stereocontrol exerted by ketones **1–3**. It is worth mentioning that virtually a single isomer is obtained in many cases (see eq 2, 5, 6, and 7 in Scheme 2).[9,10] Remarkably, an outstanding stereocontrol is achieved both in matched and mismatched pairs based on ketone **2** when the process is carried out in the presence of an additional equivalent of $TiCl_4$ (see eq 5 and 6 in Scheme 2). As expected, the less selective process involves $TiCl_4$-mediated aldol reaction of benzyloxy ketone **2** and aldehyde **4**, which gives the mismatched Felkin adduct **7** in a poor diastereomeric ratio (dr 70:30).[4,11] With the exception of this case, appropriate choice of the protecting group (ketones **1–3**) and the enolization procedure permits all the stereochemical relationships described in Scheme 1 to be obtained. Therefore, these double stereodifferentiating aldol reactions give access to a wide array of enantiopure intermediates useful for stereoselective syntheses.



Scheme 1

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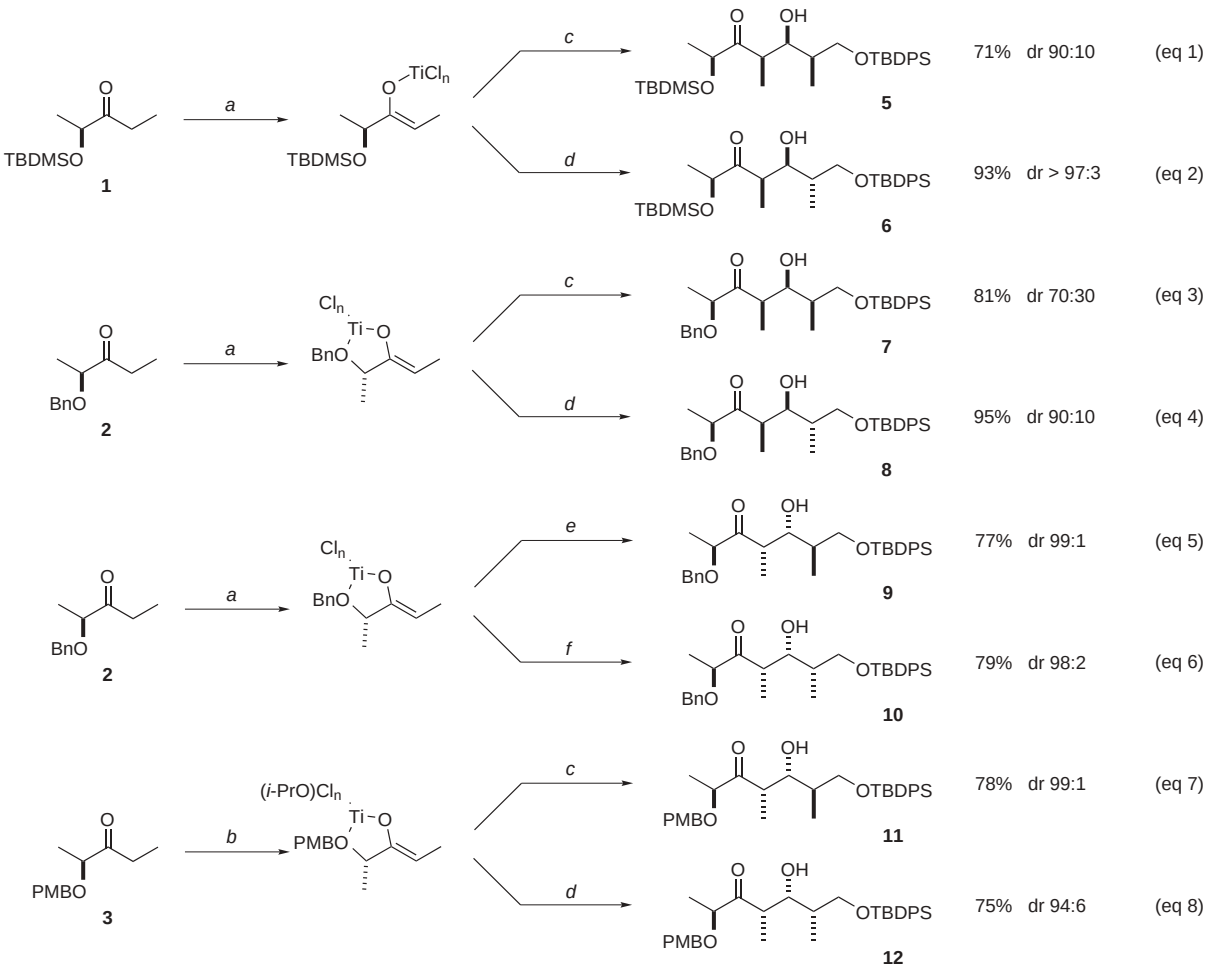


Scheme 2[12] *Reagents and conditions*: (*a*) $TiCl_4$ (1.1 equiv), *i*-Pr_2NEt (1.1 equiv), CH_2Cl_2, –78 °C, 1.5 h; (*b*) (*i*-PrO)$TiCl_3$ (1.1 equiv), *i*-Pr_2NEt (1.1 equiv), CH_2Cl_2, –78 °C, 1.5 h; (*c*) **4** (1.5 equiv), –78 °C, 45 min; (*d*) ***ent*-4** (1.5 equiv), –78 °C, 45 min; (*e*) $TiCl_4$ (1 equiv), **4** (1.5 equiv), –78 °C, 45 min; (*f*) $TiCl_4$ (1 equiv), ***ent*-4** (1.5 equiv), –78 °C, 45 min.

The utility of these double asymmetric processes has been already demonstrated in the construction of the C18–C27 fragment of superstolide A through the stereoselective reaction of ketone **3** and aldehyde **4** (see eq 7 in Scheme 2).[13] Looking for a more challenging case, we noticed that the 4,5-*syn*-5,6-*syn* relationship (see Scheme 1) present in aldol **10** (see eq 6 in Scheme 2) would be a key function in accessing an advanced intermediate in the synthesis of erythromicins A and B.

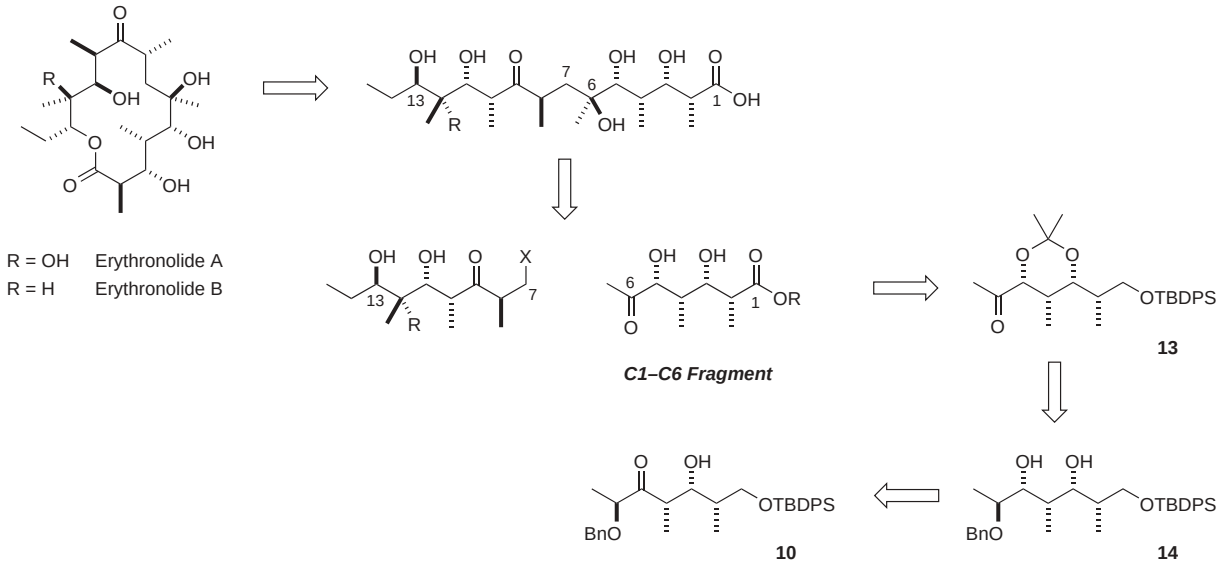
The well known antibiotic macrolides erythromicins A and B have attracted much attention because of their important biological activity and their complex structure, which contains most of the stereochemical motifs present in the polypropionate-like natural products. Therefore, total syntheses of both macrolides and their corresponding aglycones, namely erythronolides A and B, have become one of the cornerstones in organic synthesis for the last decades and have stimulated the development of new concepts and reactions for acyclic stereocontrol.[14,15]

Many of the retrosynthetic analyses applied to the seco-acids of erythronolides A and B choose the C6–C7 bond as strategic disconnection, which confers to the C1–C6 fragment a crucial role in the overall strategy. Thus, it is not surprising that methyl ketones such as that represented in Scheme 3 have been considered as surrogates of advanced C1–C6 intermediates and have concentrated the synthetic efforts of many groups.[16]

As already mentioned, a close inspection of the stereochemical array embodied in such systems suggested that three of their stereocenters might be easily installed through a double asymmetric aldol process. Particularly, ketone **13** (see Scheme 3) reported by Stork[16a] and Yonemitsu[16f] attracted our attention because its synthesis might rely on the highly stereoselective titanium-mediated aldol reaction represented in eq 6 of Scheme 2.

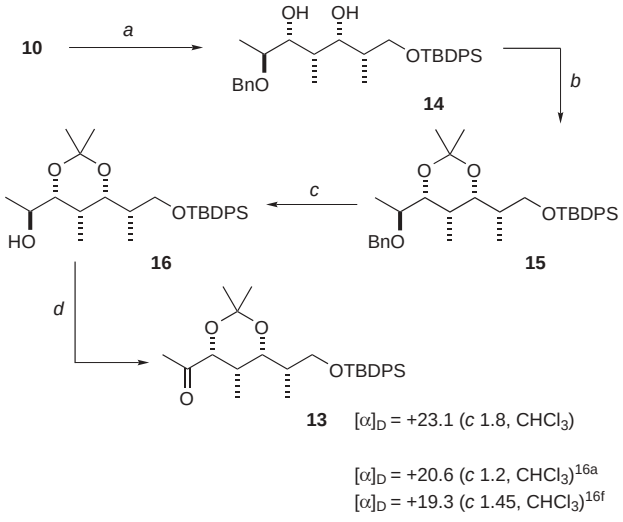
In fact, our retrosynthetic analysis anticipated that methyl ketone **13** would be available from diol **14** after a protection-deprotection sequence and final oxidation. Eventually, stereoselective reduction of aldol **10** would render the desired diol (see Scheme 3).

Thus, such a synthetic sequence should permit us to obtain **13** in a highly economic and straightforward manner taking advantage of the substrate-controlled aldol process that was previously developed.



Scheme 3

According to this approach, aldol **10** was routinely prepared in 80% yield and 98:2 diastereomeric ratio on 5 mmol scale using 1.2 equivalents of aldehyde ***ent*-4**. Surprisingly, subsequent stereoselective *syn* reduction proved to be more elusive. Initial attempts based on Narasaka–Prasad and zinc borohydride procedures[17,18] afforded diol **14** in 95% yield but in a poor diastereomeric ratio (dr 86:14 and 50:50, respectively). Fortunately, a highly stereoselective reduction (82%, dr 96:4) was finally achieved with di*iso*butylaluminium hydride at –78 °C (see Scheme 4).[19] Protection of the diastereomeric mixture furnished pure isopropylidene acetal **15** in 90% yield.[20]



Scheme 4 *Reagents and conditions*: (*a*) DIBALH, THF, –78 °C, 82%; (*b*) cat. PPTS, $(MeO)_2CMe_2$–CH_2Cl_2 1:1, r.t., 90%; (*c*) H_2, 10% Pd/C, EtOAc, r.t., 91%; (*d*) DMP, CH_2Cl_2, 0 °C, 97%.

Subsequently, removal of the benzyl group[21] and Dess–Martin periodinane oxidation of the resulting alcohol afforded the desired ketone **13**[22] in five steps and 51% overall yield from ketone **2**.

In summary, highly stereoselective titanium-mediated aldol reactions based on chiral ketones derived from lactic acid, **1**–**3**, and α-methyl-β-OTBDPS chiral aldehydes, **4** and ***ent*-4**, have been documented. Making the most of these double stereodifferentiating processes, a new approach to the construction of a fully protected C1–C6 fragment of erythronolides has been disclosed. The stereoselective sequence proceeds over five steps in 51% overall yield, which proves the synthetic potentiality of the aforementioned methodology even in the case of a reluctant 4,5-*syn*-5,6-*syn* relationship.

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(20) The relative 3,4-*syn*-4,5-*syn* configuration was secured by NMR studies of the dioxane moiety.

(21) Unexpectedly, this step turned out to be troublesome. Debenzylation with $Pd(OH)_2$/C was sluggish in EtOAc and afforded a complex mixture in MeOH. Better results (60% yield) were obtained with 10% Pd/C in EtOH, although it was not possible to prevent partial removal of acetonide protecting group and the corresponding triol was produced in 25% yield. Finally, alcohol **16** was isolated in excellent yield (91%) after 3 h in EtOAc.

(22) Physical and spectroscopic data of ketone **13** are in agreement with those previously reported. See ref. 16a, 16f. Compound **13**: colorless oil. R_f (hexanes–EtOAc 85:15) = 0.45. $[\alpha]_D$ +23.1 (*c* 1.8, $CHCl_3$). IR (film): ν = 2933, 1717, 1111, 1017 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.54 (4 H, m, ArH), 7.43–7.36 (6 H, m, ArH), 4.22 (1 H, d, *J* = 2.5 Hz, CH_3COCHO), 3.73 (1 H, dd, *J* = 9.6 Hz, *J* = 1.9 Hz, $CHOCHCH_2OSi$), 3.57 (1 H, dd, *J* = 10.3 Hz, *J* = 4.3 Hz, CH_xH_yOSi), 3.49 (1 H, dd, *J* = 10.3 Hz, *J* = 5.7 Hz, CH_xH_yOSi), 2.12 (3 H, s, CH_3CO), 2.03–1.95 [1 H, m, $OHCCH(CH_3)CHO$], 1.83–1.78 (1 H, m, $CHCH_2OSi$), 1.48 (3 H, s, CH_3CCH_3), 1.41 (3 H, s, CH_3CCH_3), 1.06 [9 H, s, $SiC(CH_3)_3$], 1.05 (3 H, d, *J* = 6.8 Hz, CH_3CHCH_2OSi), 0.70 [3 H, d, *J* = 6.6 Hz, $OHCCH(CH_3)CHO$]. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 209.3 (C), 135.6 (CH), 135.5 (CH), 133.5 (C), 133.4 (C), 129.7 (CH), 127.7 (CH), 127.6 (CH), 99.4 (C), 79.4 (CH), 75.2 (CH), 64.9 (CH_2), 36.7 (CH), 32.4 (CH), 29.8 (CH_3), 27.0 (CH_3), 26.8 (CH_3), 19.3 (C), 19.1 (CH_3), 14.2 (CH_3), 6.5 (CH_3). HRMS (+FAB): *m/z* calcd for $C_{28}H_{41}O_4Si$ $[M + H]^+$: 469.2774. Found: 469.2762.