Asymmetric Synthesis

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Catalytic Asymmetric Synthesis of Complex Polypropionates: Lewis Base Catalyzed Aldol Equivalents in the Synthesis of Erythronolide B**

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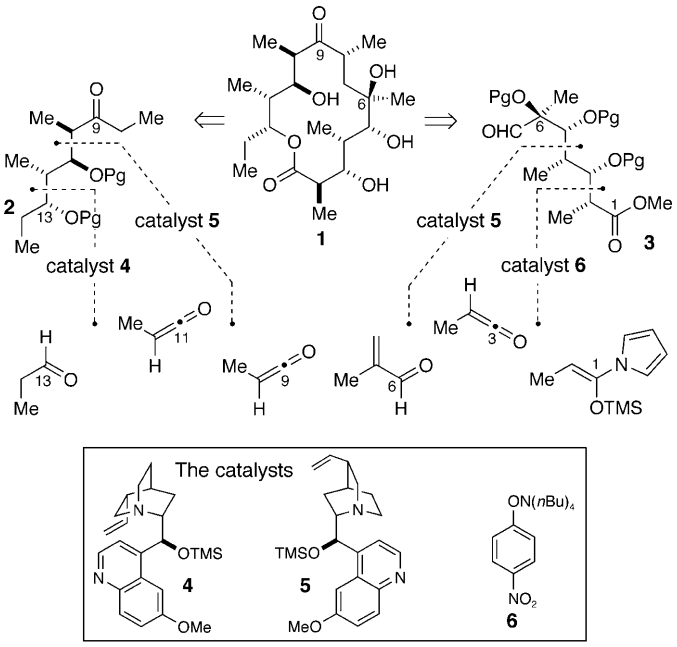
The complex stereochemical relationships and promising biological activity characterizing many members of the polyketides have spawned a wealth of reaction processes designed to facilitate the asymmetric synthesis of these natural products.[1] Among these natural products, the erythromycins have attracted special attention as test cases for evaluating these methodologies within the context of total synthesis.[2] Accordingly, we were attracted to erythronolide B as a model for developing a catalytic asymmetric synthesis of stereodefined polypropionate units that are suitable for complex molecule synthesis. Towards this goal, catalytic asymmetric ketene–aldehyde [2+2] cycloadditions serve as surrogates for asymmetric aldol additions and provide a general strategy for the catalytic asymmetric synthesis of complex polypropionate units.[3] An asymmetric formal synthesis of erythronolide B (**1**) represents a model, which illustrates the utility of catalytic asymmetric transformations to directly or indirectly establish each of the ten stereogenic centers found in the erythromycin aglycone. (Scheme 1).

Ketene–aldehyde cycloadditions represent surrogates for catalytic asymmetric aldol additions by exploting ketenes as enolate equivalents.[4] Extrapolation of this reaction design towards a strategy for catalytic asymmetric synthesis of polypropionates implicates iterative catalyst-controlled coupling of methylketene units as the means for chain elongation of the propionate unit. A synthesis of erythronolide B predicated on this analysis emerges by disconnecting the aglycone across the C1–O13 and C7–C8 bonds to reveal two modified propionate trimer equivalents **2** and **3**. The *syn*,*anti*,*syn* synthon **2** correlates to sequential catalyst-controlled methylketene coupling with propionaldehyde using the alkaloid catalysts **4** and **5**. The *all-syn* synthon **3** would be derived from the alkaloid-catalyzed cyclocondensation of methacrolein with methylketene; ensuing homologation of the resulting C6–C7 *syn*-propionate unit would exploit simple substrate-based stereocontrol utilizing achiral catalyst **6** to mediate a highly Felkin-selective Mukaiyama aldol homologation.



Scheme 1. Catalytic asymmetric synthesis of erythronolide B. TMS = trimethylsilyl, Pg = protecting group.

Synthesis of the C8–C15 synthon **2** commenced with the cyclocondensation of propionyl chloride with propionaldehyde catalyzed by *O*-trimethylsilylquinidine (**4**) and provided β-lactone **7**, which represents the C12–C13 *syn*-propionate unit (74%, 98% *ee*, ≥98% *de*; Scheme 2).[4b] Lactone **7** was then modified to allow further propionate chain elongation by its conversion into the β-hydroxy aldehyde **8** through a two-step sequence: 1) thiolate-mediated ring opening and in situ alkoxide silylation; 2) DIBAL-mediated thioester reduction (86% for 2 steps). Further homologation of **8** with methylketene, now using the quinine-based catalyst **5**, provided the targeted propionate trimer equivalent with *syn*,*anti*,*syn* linkage in the form of β-lactone **9** (95%, >95% *de*). The conversion of β-lactone **9** into ethyl ketone **11** was carried out by employing *N*,*O*-dimethylhydroxylamine, which mediated the β-lactone ring opening, and subsequent EtMgBr addition to the derived amide **10** afforded the ethyl ketone **11**.[5] Conversion of the hydroxyl group at C11 into the PMB ether was best accomplished using (*p*-methoxybenzyl)trichloroacetimidate and a substoichiometric amount of the

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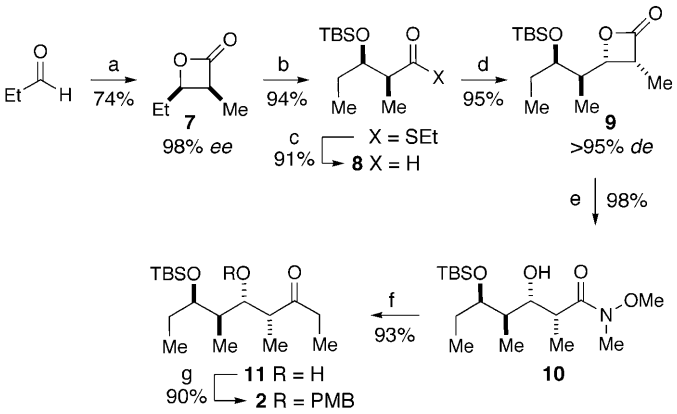
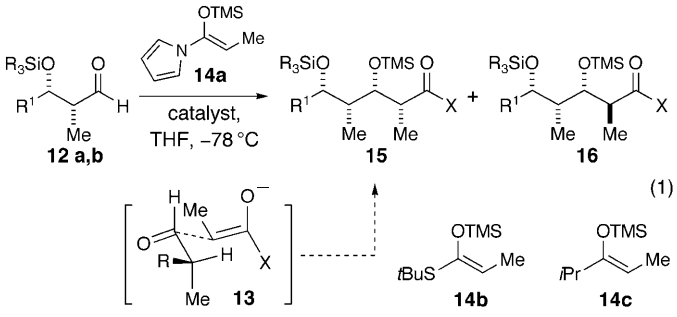


Scheme 2. Synthesis of the C8–C15 synthon **2**. Reagents and conditions: a) **4** (10 mol%), EtCOCl, iPr_2NEt, $LiClO_4$, −78 °C; b) EtSH, KHMDS (10 mol%), THF; TBSOTf, 2,6-lutidine; c) DIBAL, CH_2Cl_2, −78 °C; d) **5** (10 mol%), EtCOCl, iPr_2NEt, LiI, −78 °C; e) MeO(Me)NH_2Cl, Me_2AlCl, CH_2Cl_2; f) EtMgBr, THF; g) PMBOC(NH)CCl_3, $BF_3{\cdot}Et_2O$ (15 mol%), CH_2Cl_2. DIBAL = diisobutylaluminum hydride, HMDS = hexamethyldisilazane, PMB = *p*-methoxybenzyl, TBS = tert-butyldimethylsilyl, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl.

Lewis acid BF_3, thus affording the completed C8–C15 fragment **2** (52% yield over 7 steps).[6]

Despite the close structural homology that exists between synthons **2** and **3**, the *all-syn* relative configuration present in **3** suggested a complementary strategy for propionate assembly relative to that employed for the completion of **2**. Cinchona-alkaloid-catalyzed methylketene–methacrolein coupling would provide uneventful access to the requisite C4–C5 *syn* building block **12**. We reasoned that securing rigorous Felkin facial control in the enolate additions to **12**, ideally via open transition state **13**, would deliver the necessary *all-syn* unit without the intervention of chiral catalysts or auxiliary stereocontrol devices [Eq. (1)].[7] Literature precedent, however, suggested that oxazolidinone-derived enolates provide the method of choice for accessing *all-syn* dipropionate units, thus indicating that simple aldehyde-based diastereoselection is insufficient for achieving high Felkin selectivity.[8]



(1)

The preceding analysis suggested that Mukaiyama-type aldol reactions could be candidates for accessing the requisite Felkin facial bias from enolate additions to α-substituted aldehydes.[9] Considering that Lewis acid mediated Mukaiyama aldol reactions afforded modest diastereoselectivity in the homologations of *syn*-disubstituted aldehydes, we considered the potential for Lewis base catalyzed variants to provide the requisite aldol diastereoselectivity.[10] Given the paucity of data regarding the applicability of Lewis base catalysis to diastereoselective Mukaiyama aldols, our initial investigations were directed towards establishing the validity of this reaction design.

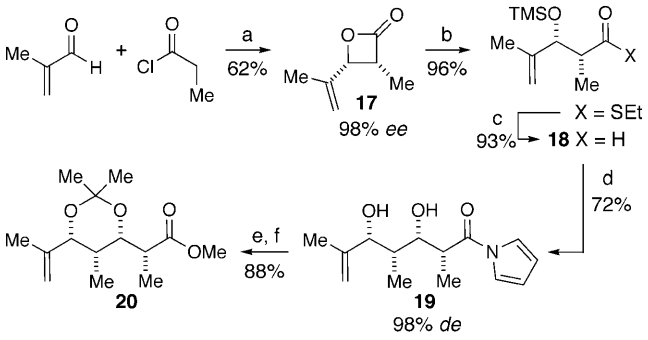
Thus, we evaluated the stereochemical outcome of Lewis base catalyzed enol silane additions to chiral α-substituted aldehydes. The results revealed that acylpyrrole-derived enol silanes in combination with phenoxide-based catalysts delivered *all-syn* selective aldol adducts. Aldehyde **12a** (R = $(CH_2)_2$Ph) and enol silane **14a** were treated with tetra-*n*-butylammonium *p*-nitrophenoxide (20 mol% of catalyst **6** was used)[11] and afforded the *all-syn* propionate trimer **15** with high diastereoselectivity (**15**/**16** = 98:2; Table 1, entry 2). The efficient silyl-group transfer from the enolate group to the emergent aldolate oxygen atom accompanied the aldol addition (Table 1, entry 1). Control experiments revealed that *p*-nitrophenoxide possesses the correct Lewis basicity to promote efficient enol silane addition without affecting base-promoted epimerization of the α-substituted aldehydes. Reaction efficiency was eroded significantly using the stoichiometric quantities of boron trifluoride required to achieve complete conversion (Table 1, entries 4 and 5). Similarly, enol silane **14a** exhibited unique reactivity in the phenoxide-catalyzed aldols, as the ketene acetal **14b** and ketone-derived enol silane **14c** were not compatible reaction partners (Table 1, entries 5 and 6).

Table 1: Phenoxide-catalyzed aldol additions of *N*-acyl pyrrole-derived enol silanes, see [Eq. (1)].

Entry	**12**, R[a]	Enol silane	Catalyst[b]	X	**15**/**16** (yield [%])[c]
1	**12a**,C(CH_2)Me	**14a**	**6**	NC_4H_4	99:1 (73)
2	**12b**,CH_2CH_2Ph	**14a**	**6**	NC_4H_4	98:2 (80)
3	**12b**	**14a**	BF_3[d]	NC_4H_4	83:17 (66)
4	**12b**	**14b**	BF_3[d]	S*t*Bu	50:50 (68)
5	**12b**	**14b**	**6**	–	n.r.
6	**12b**	**14c**	**6**	–	n.r.

[a] R_3Si = TMS (entry 1) or TBS (entries 2–6). [b] Catalyst (20 mol%) was used except as noted. [c] Diastereomer ratios were determined by GC analysis (see the Supporting Information). [d] $BF_3{\cdot}OEt_2$ (1.0 equiv). n.r. = no reaction

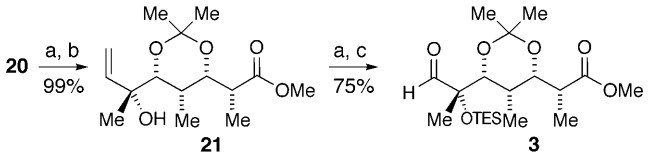
Next, assembly of the C1–C7 subunit **3** was investigated, and began with the cyclocondensation of propionyl chloride with methacrolein catalyzed by *O*-trimethylsilylquinine (**5**), thus affording the volatile β-lactone **17** (62%, 98% *ee*, *syn*/*anti* ≥ 98:2; Scheme 3). Conversion of the β-lactone into the aldehyde was again accomplished by the thiolate-ring opening/thioester reduction sequence, and afforded *syn* aldehyde **18** (89% over 2 steps).Homologating **18** with enol silane **14a** (20 mol% of catalyst **6** was used) afforded, after acidic work-up, the *all-syn* aldol adduct **19** (78%, d.r. 99:1). The crucial role played by cyclic ketal protecting groups in facilitating eventual seco-acid macro-



Scheme 3. Synthesis of *all-syn* propionate trimer **20**. Reagents and conditions: a) **5** (10 mol%), *i*Pr_2NEt, LiI, −40°C; b) EtSH, KHMDS (10 mol%), THF; TBSCl and Et_3N; c) DIBAL, CH_2Cl_2, −78°C; d) **14a**, **6** (20 mol%), THF, −70°C; then 1 N HCl; e) $Me_2C(OMe)_2$, CSA (0.05 mol%); f) NaOMe, MeOH, 0°C. CSA = camphorsulfonic acid.

lactonization requires that diol **19** be engaged as the corresponding cyclic dimethyl ketal.[12] Potential incompatibility of the electron-rich pyrrole ring with ensuing oxidative reaction conditions dictated that the acyl pyrrole group would be transformed into methyl ester **20** in advance of completing the C1–C7 unit (83% over 2 steps).

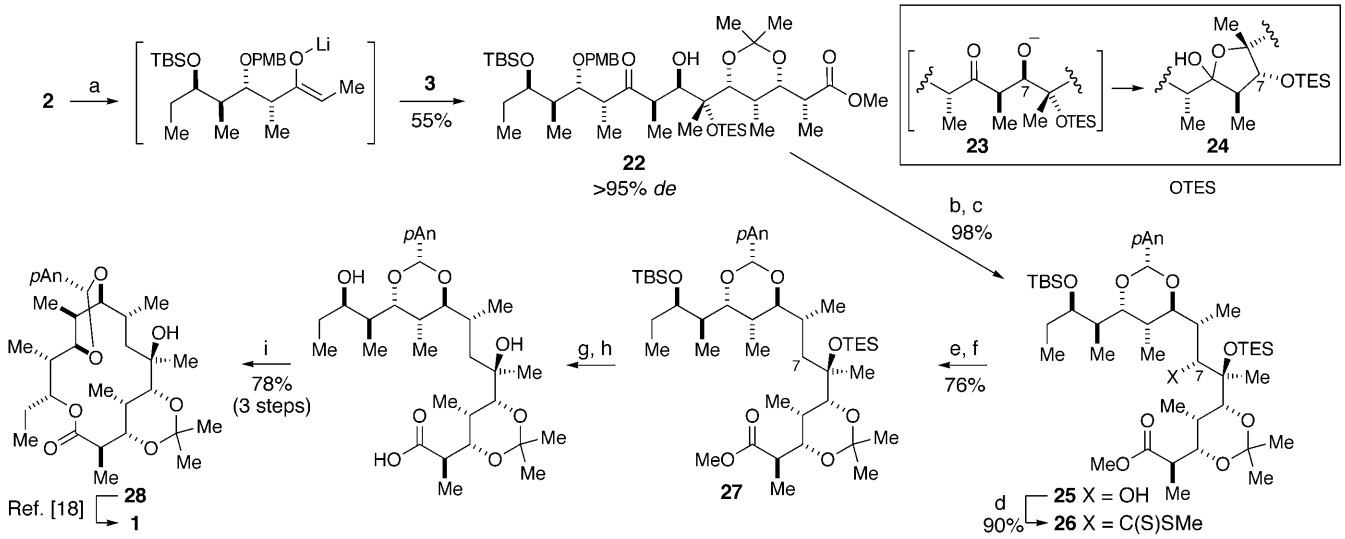
At this juncture, completion of the C1–C7 synthon necessitated a one carbon chain homologation of **20** with



Scheme 4. Synthesis of the C1–C7 synthon **3**. Reagents and conditions: a) O_3, CH_2Cl_2, −78°C; then Me_2S; b) $CH_2CHMgBr$, THF, −78°C; c) TESOTf, 2,6-lutidine. TES = triethylsilyl.

concomitant installation of a tertiary alcohol at C6. To this end, oxidative cleavage of the alkene group preceded Felkin-selective vinyl Grignard addition to the resulting methyl ketone, which delivered tertiary alcohol **21** (99%, 100% *de*; Scheme 4).[13] Unveiling the newly installed terminal olefin as the corresponding aldehyde, and protection of the tertiary alcohol, completed the C1–C7 synthon in the from of aldehyde **3**.

Coupling fragments **2** and **3** to secure the erythronolide carbon framework was predicated on correctly establishing the unaddressed C8 stereocenter (Scheme 5). To this end, the kinetic *Z*-lithium enolate of ethyl ketone **2** was treated with aldehyde **3,** and afforded β-hydroxy ketone **22** as a single *syn*-aldol diastereomer (55%; 90% based on recovered **2**).[14] Successful fragment coupling was dependent on quenching the incipient aldolate intermediate **23** with a soluble proton source (AcOH) at low temperature; warming the aldolate or attempted quenching using aqueous solutions at low temperature led to silyl-group migration and irreversible formation of lactol **24**. Hydroxy-directed reduction of the ketone (≥97% *de*) delivered the *S* alcohol at C9, and allowed the PMB ether at C11 to be engaged as the C9–C11 *p*-anisyl acetal **25** (98% over 2 steps).[15] Deoxygentaion of the alcohol at C7 was carried out using the conditions developed by Evans et al., providing that formation of xanthate **26** was achieved at low temperature (−78°C) to circumvent the aforementioned silyl-group migration.[14b,16] Deoxygenation was accompanied by epimerization of the acetal stereocenter (ca. 2.4:1), thus necessitating that the desired configuration be re-established from the crude mixture of diastereomers (4-$MeOC_6H_4CH(OMe)_2$, H^+) to secure **27** (68% over 3 steps). Ester saponification, removal of the silyl ether, and subsequent macrolactonization using modified Yamaguchi conditions,[17] afforded the protected (9*S*)-dihydroerythronolide B **28** (78% over 3 steps). Macrolactone **28** represents the completion of our formal synthesis, as this same material had



Scheme 5. Fragment coupling and macrolide construction. Reagents and conditions: a) LiHMDS, THF, −78°C, **3**; then AcOH, −78→23°C; b) $Zn(BH_4)_2$, Et_2O; c) DDQ, CH_2Cl_2; d) KHMDS, CS_2, MeI, −78°C; e) AIBN, nBu_3SnH; f) 4-$MeOC_6H_4CH(OMe)_2$, CSA (0.05 mol%); g) LiOH, THF/MeOH (1:1) , 55°C; h) $(nBu)_4NF$, THF, 65°C; i) 2,4,6-$(Cl_3C_6H_2)COCl$, DMAP, Et_3N, C_6H_6. AIBN = azabis(isobutyro)nitrile, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMAP = 4-dimethylaminopyridine, *p*An = *p*-anisyl. For the conversion of **28** into **1** see Ref. [18].

previously provided a route to the erythromycin aglycone framework (in 4 steps).[18]

Lewis base catalyzed aldol equivalents provide direct access to eight, and indirect access to the remaining three of the eleven stereocenters, which render erythronolide B an enduring test case for asymmetric synthetic methods. This formal synthesis of erythronolide B highlights the efficient access to complex polypropionate architectures, which are afforded by asymmetric catalysis using easily obtained, enantioenriched, and achiral Lewis basic catalysts.

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