tivity was completely opposite to that for the alcohol addition to common silaethenes, which indicates the significant contribution of the resonance form **B** in **1b** (Scheme 1); the OH hydrogen and methoxy groups of methanol were bonded to the unsaturated silicon atom and a ring carbon atom in **1b**, respectively.[16]

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[8] **1b**: Yellow crystals; m.p. 95 °C (decomp.); ^{1}H NMR (300 MHz, [D$_6$]benzene, TMS): $\delta = 0.47$ (s, 12H), 1.16 (s, 18H), 1.17 (s, 18H); ^{13}C NMR (75 MHz, [D$_6$]benzene, TMS): $\delta = 0.2$, 19.6, 28.5, 28.6, 32.9, 157.0 (C=C), 159.9 (Si=C, $^1J_{Si,C} = 66$ Hz); ^{29}Si NMR (59 MHz, [D$_6$]benzene, TMS): $\delta = -71.9$ (Si=C, $^1J_{Si,C} = 66$ Hz), 1.7 (Si*t*BuMe$_2$); HRMS calcd for $C_{23}H_{48}Si_3$ 408.3064 found 408.3060.

[9] Typical δ_{Si} values for $(Me_3SiO)(Ad)C{=}Si(SiMe_3)_2$ (Ad = adamantyl) and $(Me_3Si)(t BuMe_2Si)C{=}SiMe_2$ are +42 and +144, respectively.[10] Recently, negative δ_{Si} values for the unsaturated silicon nuclei have been found in 1-aza-3-silaallene ($\delta_{Si} = -57$)[11] and hexaphenylsilacalicene ($\delta_{Si} = -28$),[5] with rather less polar Si–C double bonds.

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[12] Recrystallization of **1b** from heptane gave single crystals suitable for X-ray structural analysis. X-ray analysis of **1b**: $M_F = C_{23}H_{48}Si_3$, $M_W = 408.89$, monoclinic, space group $P2_1/c$, $a = 11.0141(8)$, $b = 17.9026(9)$, $c = 14.210(3)$ Å, $\beta = 91.173(2)^\circ$, $V = 2801.4(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 0.969$ g cm^{-3}, $\mu(Mo_{K\alpha}) = 1.75$ cm^{-1}. The reflection intensities were collected on a Rigaku/MSC Mercury CCD diffractometer (50 kV, 40 mA) with graphite monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71069$ Å) at 150 K. The structure was solved by direct methods, by using SIR-92, and refined by full-matrix least-squares analysis on *F*. A total of 6392 reflections were measured, and of these, 4509 reflections [$F_o > 3.00\sigma(F_o)$] were used in refinement: $R = 0.041$, $Rw = 0.044$. CCDC-175782 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

[13] The bend angles θ and γ are defined as the angles between the three-membered-ring plane and the Si(unsaturated)–C bond, and between the R_2Si plane and the Si(unsaturated)–C bond, respectively (Scheme 2). Theoretical bend angles θ and γ for **1c** in the bent structure are 171.8 and 141.5°, respectively.[3g]

[14] The reaction of **1b** with *tert*-butyl alcohol in hexane under reflux afforded the alcohol adducts of the corresponding silacyclobutadiene as expected.[2] Details will be reported elsewhere.

[15] **3**: a colorless oil; ^{1}H NMR (300 MHz, C_6D_6): $\delta = 0.21$ (s, 3H), 0.25 (s × 2, 6H), 0.27 (s, 3H), 1.00 (s × 2, 18H), 1.18 (s, 9H), 1.22 (s, 9H), 3.02 (s, 3H), 4.24 (s, 1H); ^{13}C NMR (75 MHz, C_6D_6): $\delta = -2.92$, -2.87, -2.60, -2.41, 18.51, 18.59, 27.65, 29.41, 30.51, 32.73, 38.09, 53.95, 76.42, 115.25, 156.53; ^{29}Si NMR (59 MHz, C_6D_6): $\delta = -90.24$ (d, ^1J(Si,H) = 155 Hz), -1.92, -1.43; MS (70 eV) *m*/*z* (%) 425 ($M^+ - 15$, 6), 259 (6), 147 (100), 115 (6).

[16] Similar inverted regioselectivity has been observed for a silacalicene by West et al.[5]

Aldolase-Catalyzed Asymmetric Synthesis of Novel Pyranose Synthons as a New Entry to Heterocycles and Epothilones**

Junjie Liu and Chi-Huey Wong*

The enzyme 2-deoxyribose-5-phosphate aldolase (DERA, EC 4.1.2.4), a Schiff base forming type I class aldolase, catalyzes the reversible aldol reaction of acetaldehyde and D-glyceraldehyde 3-phosphate (G3P) to form D-2-deoxyribose-5-phosphate (DRP).[1] The enzyme has been overexpressed in *Escherichia coli*, and its structure and catalytic mechanism have been determined at the atomic level.[2]

DERA accepts a broad range of acceptor and donor aldehydes in addition to the natural substrates.[1] An interesting transformation is the sequential asymmetric aldol addition reaction of three achiral aldehydes to form pyranoses with two new stereogenic centers (Scheme 1 A).[3] In this sequential reaction, the first aldol product acts as a substrate for the second aldol reaction to give an enantiomerically pure 3,5-

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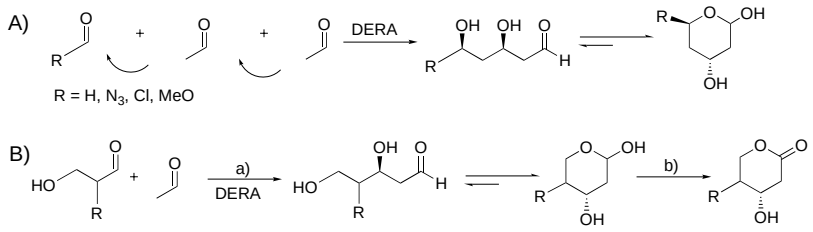
Supporting information for this article is available on the WWW under http://www.angewandte.com or from the author.

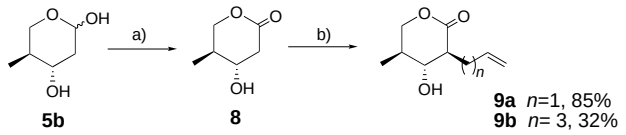


Scheme 1. Preparation of unnatural pyranoses with DERA. a) pH 7.5, DERA, acetaldehyde; b) Br_2, $BaCO_3$. For details of routes A and B see text.

dihydroxyaldehyde which then cyclizes to form the stable pyranose, thus driving the reaction toward condensation. Since these 1,3-polyol systems are useful synthons,[4] we have further examined the scope of this enzymatic methodology. Our strategy is to exploit β-hydroxyaldehydes as acceptors (Scheme 1B) to generate the products which would cyclize to form stable hemiacetals, thus driving the reaction toward condensation. The hemiacetal could be further oxidized to give a lactone. We have found that the oxidation sometimes makes the purification much easier, and more importantly, the lactone can be further transformed to other useful synthons. Several different substrates have been tested and the results are summarized in Table 1.

The configuration of C2 in the acceptor aldehydes is very critical for the enzymatic reaction. We found that D isomers were overwhelmingly preferred over L isomers when polar groups (e.g. OH, N_3) were at this position; when racemic acceptor aldehydes were used, only the D isomer products were formed (Table 1, entries 2–4). On the contrary, an opposite enantioselectivity was observed when a hydrophobic group is at the C2 position (Table 1, entries 5–7): **5a** afforded lactone **5b** in 48% yield after two steps, while its enantiomer **6a** only gave **6b** in trace amounts, and racemic aldehyde **7a** only produced **7b**. Molecular modeling based on the structure of DERA[2] reveals a hydrophilic binding pocket composed of Thr170 and Lys172 for the OH group at C2 and a hydrophobic pocket for the H atom at C2. A switch of the binding was observed for **5a** and **7a** in which the methyl and the methoxy groups are in the hydrophobic pocket, which results in the change of enantioselectivity.

The 1,3-polyol systems prepared from the enzymatic reaction could serve as useful synthons.[5–8] An example is the stereoselective C2 alkylation of β-hydroxylactone with an alkyl bromide under chelation control directed by the β-hydroxy group (Scheme 2).[9] This reaction can provide more diversified pyranoses after reduction of the lactones[10] and generate additional useful intermediates for organic synthesis. In our alkylation experiment, the other diastereomers were not detected. The relative configuration of **9a** was unequivocally confirmed by NMR experiments.



Scheme 2. Stereoselective alkylation. a) Br_2, $BaCO_3$, 12 h, 62%; b) LDA, HMPA, $-78\,^{\circ}C$, alkene bromide, 36 h. LDA = lithium diisopropylamide, HMPA = hexamethylphosphoramide.

Table 1. Aldol condensation catalyzed by DERA.

Entry	Acceptor	Donor	t [days]	Product	Yield [%]
1	**1a**		3	**1b**	65
2	**2a**		3	**2b**	60[a]
3	**3a**		3	**3b**	47[a]
4	**4a**		6	**4b**	28[a]
5	**5a**		3	**5b**	48[b]
6	**6a**		6	**6b**	trace[b]
7	**7a**		6	**7b**	22[a]

[a] Based on the reactive enantiomers. [b] Total yield for two steps from protected aldehyde.

The availability of both intermediates **9a** and **9b** permitted us to choose either the Suzuki coupling[11a,b,k–n] or olefin metathesis strategy[11c–h,p,q] to prepare epothilones as potential anticancer agents.[12] Since allyl bromide is more active and gives **9a** in a higher yield, the Suzuki coupling strategy was chosen for the construction of the C12–C13 Z double bond (Scheme 3). In addition to **9a**, compound **11** prepared by DERA was also used as a key synthon.[13]

In our synthesis of fragment **A** (Scheme 4), the lactone ring of **9a** was first opened to afford diol **12**, which was then protected as the PMP acetal. After reduction by $LiAlH_4$, the hydroxy was removed by mesylation followed by reduction, both in excellent yield.[14] Regioselective cleavage of the PMP protecting group in **13** with DIBAL in toluene gave the primary alcohol as the only product, which was oxidized with Dess–Martin periodinane[15] to give aldehyde **14**. Compound **14** was then condensed with *tert*-butyl isobutyrylacetate[11b, 16] to give compound **15** in 70% yield (d.r. 8:1). Stereoselective reduction with $Me_4NBH(AcO)_3$[17] resulted in the formation of the desired diol (d.r. 10:1). Regioselective silylation of the β-hydroxy group followed by oxidation gave fragment **A**.

Because the configuration of C2 in **16** is not essential in our synthetic route (Scheme 5), racemic lactaldehyde acetal **16** was used in our current synthesis. Interestingly, we found that only the D isomer was accepted as a substrate for DERA and no L isomer product was detected in our experiment.

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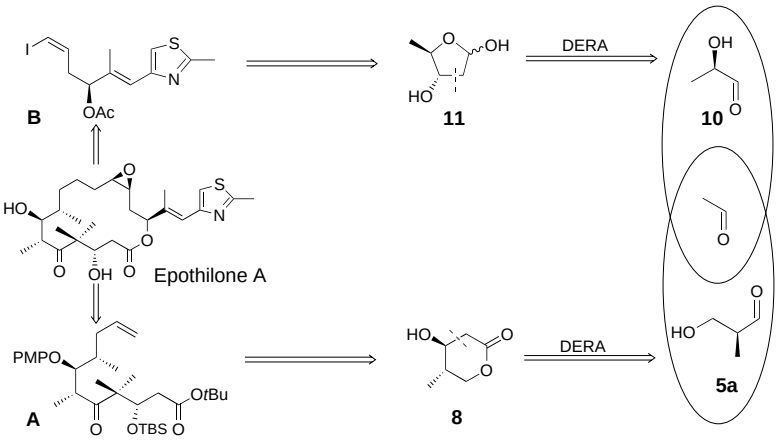
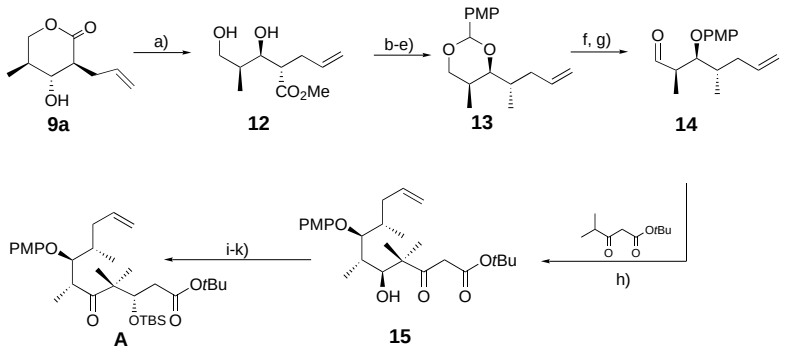
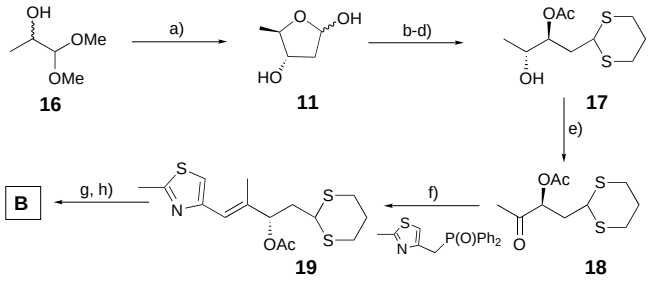


Scheme 3. Retrosynthesis of epothilone A and C. PMP = 4-methoxyphenyl, TBS = *tert*-butyldimethylsilyl.



Scheme 4. Synthesis of fragment **A**. a) MeONa, −30 °C, 60 %; b) anisaldehyde dimethyl acetal, CSA, 95 %; c) $LiAlH_4$, 0 °C – RT, 90 %; d) MsCl, NEt_3, 94 %; e) $LiAlH_4$, 88 %; f) DIBAL, toluene, 93 %; g) Dess-Martin oxidation, 96 %; h) NaH, *n*BuLi, 0 °C, 70 %; i) $Me_4NBH(OAc)_3$, −30 °C, 83 %; j) TBSOTf, 2,6-lutidine, 0 °C, 10 min, 100 %; k) Dess–Martin oxidation, 3 h, 90 %. CSA = 10-camphorsulfonic acid, PMP = 4-methoxyphenyl, Ms = mesyl = methanesulfonyl, DIBAL = diisobutylaluminum hydride, TBS = *tert*-butyldimethylsilyl, Tf = triflate = trifluoromethanesulfonyl.



Scheme 5. Synthesis of fragment **B**. a) Dowex(H^+), 40 °C, then pH 7.5, DERA, acetaldehyde, three days, 38 % (two steps based on the D enantiomer); b) AcCl, pyr, 95 %; c) $BF_3 \cdot Et_2O$, H_2O/CH_3CN, 0 °C, 84 %; d) 1,3-propanedithiol, $TiCl_4$, −78 °C, 97 %; e) DMSO, $(COCl)_2$, 95 %; f) *n*BuLi, THF, −78 °C, 88 %; g) $Hg(ClO_4)_2$, $CaCO_3$, THF/H_2O, RT, 2 h; h) $Ph_3P{=}CHI$, $NaN(TMS)_2$, HMPA, THF, −78 °C. 60 % (two steps). Ac = acetyl, pyr = pyridine, DMSO = dimethyl sulfoxide, THF = tetrahydrofuran, TMS = trimethylsilyl.

The preparation of fragment **B** is rather straightforward (Scheme 5). The β-hydroxy group of **11** was selectively protected and the hemiacetal was treated with 1,3-propanedithiol to afford the dithiane **17**, which was oxidized to ketone **18** in 95 % yield. Wittig reaction of **18** with a phosphine oxide afforded **19**.[11b, 18] Following deprotection of the dithiane with $Hg(OCl_4)_2$,[19] the aldehyde product was directly coupled with $(Ph_3P^+CH_2I)I^-$[20] to afford fragment **B** in 60 % yield for the two steps.

The Suzuki coupling of fragments **A** and **B** proceeded smoothly as described by Danishefsky et al.[11b] to afford **20** (Scheme 6). After the acetyl and *tert*-butyl ester protecting groups were removed, the hydroxy acid **21** was subject to Yamaguchi macrolactonization conditions[21] to afford the intermediate **22**. The PMP and TBS protecting groups were removed with DDQ[22] and HF · pyr, respectively, to furnish epothilone C (**Epo C**). Epoxidation with a freshly prepared solution of 1,3-dimethydioxirane (DMDO)[23] afforded synthetic epothilone A (**Epo A**) with physical properties ($[\alpha]_D$, ^1H, ^{13}C NMR, MS, IR) identical to the reported data.[11g]

In summary, we have developed a new strategy for the synthesis of unnatural pyranose synthons through enzymatic reactions catalyzed by DERA. This strategy is very convergent and effective. Coupled with β-hydroxy-directed highly stereoselective alkylation, diversified 1,3-polyols can be prepared. Their application to natural product synthesis has been illustrated by the concise total synthesis of epothilones A and C.

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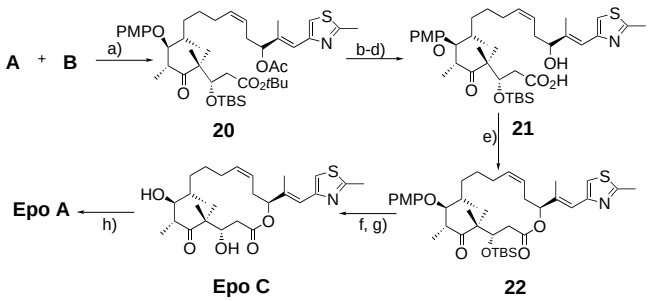

Scheme 6. Final steps for the synthesis of epothilone **A**. a) $[PdCl_2(dppf)_2]$, Ph_3As, Cs_2CO_3, 9-BBN, 65 %; b) MeONa(cat.), MeOH, 85 %; c) TMSOTf, 2,6-lutidine; d) NaOH(cat.) MeOH, 78 % for two steps; e) Yamaguchi conditions, 85 %; f) DDQ, CH_2Cl_2, 99 %; g) HF · Pyr. THF, 95 %; h) DMDO, 45 %. dppf = bis(diphenylphosphanyl)ferrocene, 9-BBN = 9-borabicyclo[3,3,1]nonane, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DMDO = 3,3-dimethyldioxirane.

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Convergent Synthesis of Silylated Allylic Alcohols by a Stereoselective Domino, Sequential Radical-Coupling Reaction**

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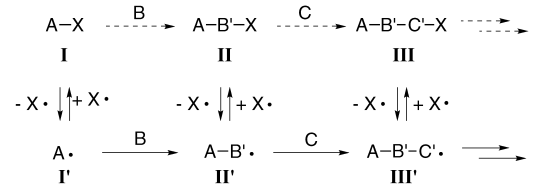
The construction of multiple carbon – carbon bonds by tandem reactions represents an efficient approach to the synthesis of complex molecular structures from simple organic building blocks.[1] Although radical-mediated intramolecular tandem cyclization exemplifies such an approach,[2] extensions to the intermolecular reaction (Scheme 1; **I'** – **III'**) have been severely limited, and require careful choice of



Scheme 1. A – X: Radical precursor; B, C: radical acceptors.

coupling partners.[3] This limitation could be attributed to the difficulty in the selective reaction of the transient radicals, for example, **I'**, **II'**, and **III'**, with certain coupling partners in radical chain reactions. The problem might be solved if we could prepare the radical intermediates **I'**, **II'**, and **III'** as their radical precursors **I**, **II**, and **III**, and subsequently couple them with radical acceptors in an atom- or group-transfer manner (Scheme 1).[4] The reaction would then be an iterative atom- or group-transfer radical reaction.[5] However, there have been no reports of such transformations, with the exception of living radical polymerization, in which the same alkenes react consecutively.[6]

We have reported the group-transfer coupling of trimethylsilyl phenyl telluride (**1**), carbonyl compounds, and isonitriles, which involves the selective carbon – carbon bond formation of the α-siloxy radical **2** with isonitriles.[7] It should be noted that the reaction of silyl tellurides with carbonyl compounds in the absence of isonitrile afforded the α-siloxy telluride **3**. This unique feature of the reaction prompted us to investigate alkynes as a third coupling partner (Scheme 2). Here we report a novel group-transfer coupling of **1**, carbonyl compounds, and alkynes to give the silylated allylic alcohol **5**. As the product also possesses a reactive carbon – tellurium bond, radical-mediated transformation via the vinyl radical **4**

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