Synthetic Methods

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# Synthesis of Polyketide Stereoarrays Enabled by a Traceless Oxonia-Cope Rearrangement**

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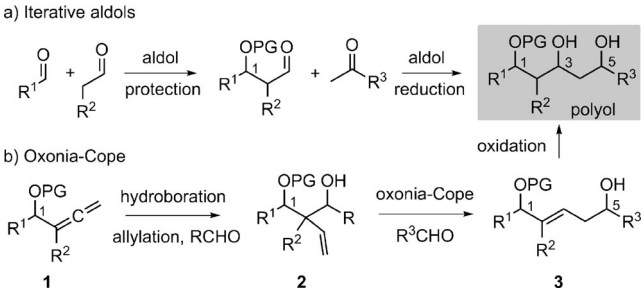
***Abstract:*** *Polyketide antibiotics bearing skipped polyols represent a synthetic challenge. A $SiCl_4$-promoted oxonia-Cope rearrangement of syn,syn-2-vinyl-1,3-diols was developed to forge an array of 1,5-pentenediols, thus providing versatile motifs for the preparation of 1,2,3,5-stereoarrays in a highly stereoselective manner. Further exploration with $Sn(OTf)_2$ realized the rearrangement of a cross-aldehyde which tactically warrants the utility of the current approach to access complex polyketides. The origin of high stereoselectivity is attributed to a chairlike anti-conformation of the oxonium ion intermediate.*

Polyketides have been a long-standing interest in the synthetic community not only because of their vastly diverse structures but also for their biological significance as antibiotics.[1] Innovative synthetic methodologies are continuously being recruited into elegant solutions to construct polyols in complex molecules.[2,3] Sophisticated chiral auxiliaries and catalytic variations as well as organocatalysis have witnessed the fruitful progress in polyketide synthesis through an iterative aldol approach.[4] Despite the abundant precedent for the preparation of these stereoarrays, a challenge encountered in these aldol approaches is to remotely control a newly formed stereocenter.[3a] For instance, additional steps such as protection and reduction are often required to assemble polyols (Scheme 1 a). Roush and co-workers orchestrated an innovative double allylboration of aldehydes with chiral bifunctional allylborane reagents to deliver 1,5-pentenediols in good yield and high enantioselectivity.[5] The sophisticated synthesis of allenyl boronate and stoichiometric chiral borane still strive for a practical alternative. We devise here a non-aldol approach[6] to construct 1,5-pentenediols (**3**), bearing versatile functional groups, through a highly stereoselective oxonia-Cope rearrangement of homoallylic alcohols.




***Scheme 1.*** Skipped polyol synthesis by an iterative aldol (a) and oxonia-Cope rearrangement (b). PG = protecting group.

The oxonia-Cope rearrangement has been recognized as a powerful synthetic method to prepare chiral homoallylic alcohols by means of an allyl transfer.[7] The leading research from the group of Nokami and others clearly shows that the rearrangement is highly stereoselective and has been successfully applied in the construction of selected natural products and chiral moieties.[7k,l] However, the efficacy of stereoinduction in complex substrates bearing inherent chirality, and their synthetic potential remain elusive. Moreover, a competing Prins cyclization and other cation-initiated skeletal rearrangements might limit its application in organic synthesis.[8] In our design, the homoallylic intermediate **2** is anticipated to form a linear structure (**3**) through an oxonia-Cope rearrangement (Scheme 1 b). The chairlike transition state in the Cope rearrangement allows us to control these challenging acyclic stereoarrays in a highly stereodefined manner. Facile and diverse transformations of the corresponding alkene in the 1,5-pentenediol **3**, as well as the ready availability of chiral allenic alcohols (**1**) render this approach synthetically attractive.[9]

With this notion in mind, we began to evaluate the feasibility of the oxonia-Cope rearrangement of racemic *syn*,*syn*-**2a** (Table 1),[10] which was readily prepared from the hydroboration of the TBS-protected α-allenic alcohol **1a** with 9-BBN and subsequent allylation of propanal.[11] In contrast to literature precedents using Brønsted acids, such as *p*-TsOH, CSA, and TfOH,[7] several undesired reactions including desilylation and ketalization, Prins cyclization, and cation-initiated rearrangements were found to occur with *syn*,*syn*-**2a**. A variety of Lewis acids were thus executed. In our hands, $BF_3{\cdot}Et_2O$, $SnCl_4$, and $TiCl_4$ promoted the rearrangement of **2a** in moderate to good conversions and the desired product **3a**[10] was isolated in a moderate yield (entries 1–3). Aluminum-based Lewis acids, such as $Et_2AlCl$

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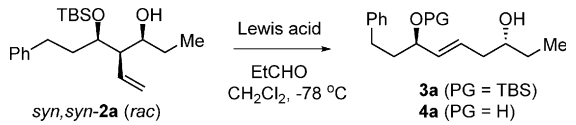
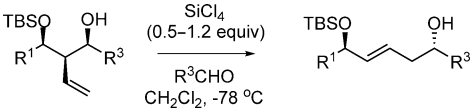
***Table 1:*** Optimization of the oxonia-Cope rearrangement of *rac*-**2a**.[a]

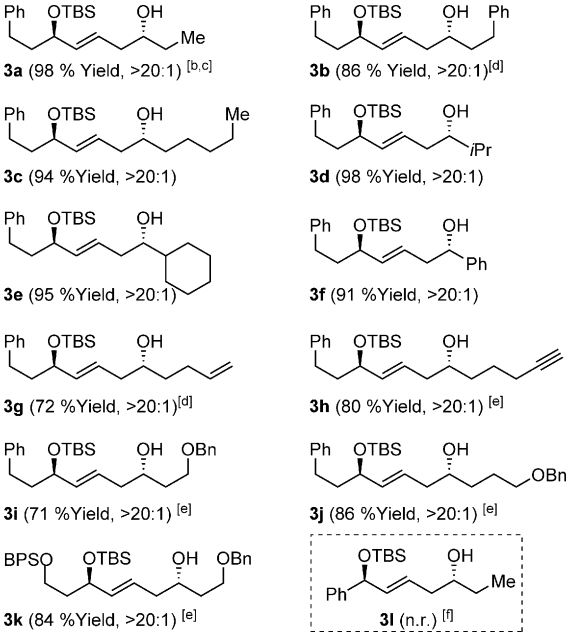



| Entry | Lewis acid | *t* [h] | Conv. [%][b] | *ds*[c] | Yield [%][d] |
|---|---|---|---|---|---|
| 1 | $BF_3{\cdot}Et_2O$ | 12 | 75 | >20:1 | 53 |
| 2 | $SnCl_4$ | 12 | 67 | n.d. | 45 |
| 3 | $TiCl_4$ | 2 | 90 | >20:1 | 60 |
| 4 | $Et_2AlCl$ | 20 | 53 | n.d. | 18 |
| 5 | $EtAlCl_2$ | 12 | 78 | n.d. | 25 |
| 6 | TMSOTf | 2 | >99 | >20:1 | 10 (20) |
| 7 | $Fe(OTf)_3$ | 16 | 27 | n.d. | 13 |
| 8 | $Zn(OTf)_3$ | 16 | n.d. | n.d. | n.d. |
| 9[e] | $Sc(OTf)_3$ | 16 | 85 | n.d. | 82 (5) |
| 10 | $Sn(OTf)_2$ | 20 | 88 | n.d. | 83 |
| 11 | $SiCl_4$ | 1 | >99 | >20:1 | 88 (5) |
| 12[f] | $SiCl_4$ | 6 | >99 | >20:1 | 90 |

[a] Reaction conditions: racemic **2a** (50 mg, 0.144 mmol), Lewis acid (1.2 equiv), EtCHO (1.3 equiv), $CH_2Cl_2$ (3 mL), −78 °C. [b] Conversion was determined by $^1$H NMR (400 MHz, $CDCl_3$) spectroscopy. [c] The determination of diastereoselectivity (HPLC) and the relative stereochemistry (Mosher's method) of *rac*-**3a** are illustrated in the Supporting Information. [d] Yield of isolated product. The desilylation product *rac*-**4a** is shown within parentheses. [e] The reaction was run at −50 °C. [f] Used 0.5 equiv of $SiCl_4$. n.d. = not determined, TBS = *tert*-butyldimethylsilyl, TMSOTf = trimethylsilyl trifluoromethanesulfonate, Tf = trifluoromethanesulfonyl.

***Table 2:*** Substrate scope for oxonia-Cope rearrangement.[a]




[a] Reaction conditions: *rac*-**2** (0.15–0.25 mmol), $SiCl_4$ (0.5–1.2 equiv), $R^3CHO$ (1.3–1.5 equiv), $CH_2Cl_2$ (3–5 mL), −78 °C, 2–8 h. [b] Yield of isolated product. [c] The diastereoselectivity (*ds*) was determined by $^1$H NMR spectroscopy. [d] The desilylation products *rac*-**4b** (13 % yield) and *rac*-**4g** (10 % yield) were isolated. [e] Yields were based on the recovered starting materials (brsm). The conversion was generally over 90 %. [f] No reaction. BPS = *tert*-butyldiphenylsilyl.

and $EtAlCl_2$, delivered **3a** in lower yield (entries 4 and 5). TMSOTf was too strong and resulted in decomposition of **2a** and the yield of isolated **3a** was inferior (entry 6). For metal triflates, $Sc(OTf)_3$ and $Sn(OTf)_2$[7] were found to be superior to ferric and zinc triflates (entries 9 and 10 versus 7 and 8). Impressively, when the weak Lewis acid $SiCl_4$ was implemented, high diastereoselectivity and yield were achieved in just 1 hour (entry 11; 5 % of the desilylated the 1,5-diol **4a** was also isolated). Under substoichiometric quantities of $SiCl_4$, the diastereoselectivity and yield remained promising while the desilylation was largely suppressed (entry 12 versus 11).

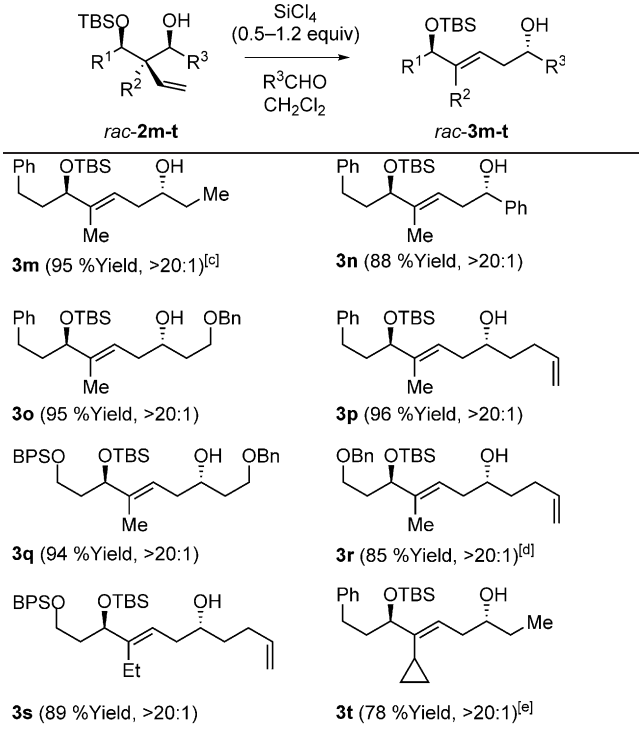
With the optimized reaction conditions in hand, substrates bearing versatile functional groups were surveyed (Table 2). The rearrangement conditions can tolerate a carbon chain (**3c**), steric hindrance (**3d** and **3e**), alkene (**3g**), alkyne (**3h**), and functional groups (**3i**, **3j**, and **3k**). All of the substrates underwent the rearrangement and resulted in good yields and excellent diastereoselectivity (*ds* > 20:1). Introducing a silylated hydroxy group on the left wing in **2k** did not hamper the efficiency of the Cope rearrangement (**3k**). When $R^1$ was a phenyl group (**3l**), the Cope rearrangement did not proceed, most likely because of the steric hindrance with $R^3$ in the chairlike transition state (see below). However, when $R^3$ was a phenyl group, the reaction proceeded smoothly and compound **3f** was obtained in excellent yield and diastereoselectivity.

The rearrangements are also applicable to 2-alkylated substrates (**2m–t**) and the corresponding 2-alkylated-1,5-pentendiols were furnished in high diastereoselectivity (Table 3). The stereochemistry of the double bond and newly formed secondary alcohol were consistent with the stereochemistry found in **3a**. It is particularly noteworthy that a cyclopropane group is tolerated during the rearrangement of **2t**. With the treatment of 0.3 equivalents of $SiCl_4$ at −78 °C, the desired product **3t** was isolated in 78 % yield (78 % conv.). The resulting vinylcyclopropane here may serve as a useful motif to construct functionalized cyclopentenes.[13]

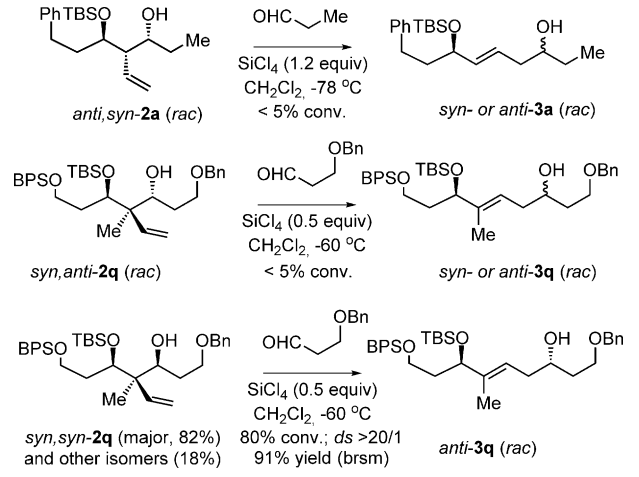
To gain insights into the origin of stereoselectivity in the oxonia-Cope rearrangement and to evaluate reactivity of minor stereoisomers of 1,3-diols, *anti*,*syn*-**2a** and *syn*,*anti*-**2q**[10] were independently prepared from a hydroboration-allylation sequence (8–15 % yield upon isolated) and subjected to the standard reaction conditions of the Cope rearrangement (Scheme 2). None of the corresponding 1,5-diols **3a** and **3q** were detected by $^1$H NMR spectroscopy, and an elevated reaction temperature (> −50 °C) resulted in desilylation and the decomposition of the 1,3-diols. Moreover, by using a crude mixture containing all stereoisomers of **2q** (82 % purity for major isomer), the subsequent rearrangement delivered the desired *anti*-1,5-pentenediol **3q** in excellent yield and high diastereoselectivity (*ds* > 20:1) and the unreactive stereoisomers were fully recovered. It indicates that the major isomer (*syn*,*syn*-**2**) of the 1,3-diols is chemoselectively preferred, and the oxonia-Cope rearrangement process is highly stereoselective.[7f]

***Table 3:*** Preparation of (*E*)-2-alkyl-1,5-pentenediols through an oxonia-Cope rearrangement.[a,b]

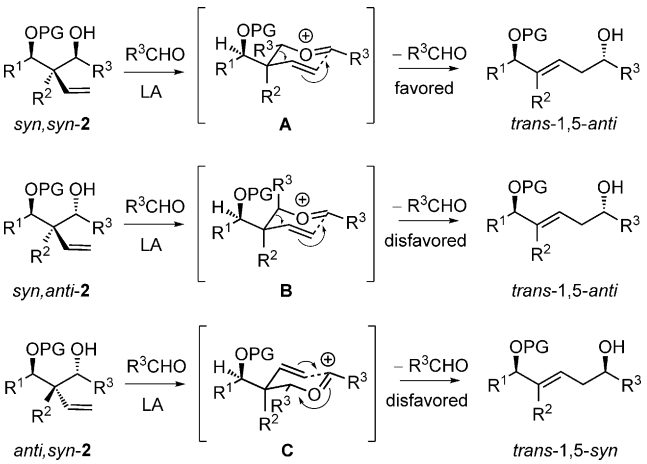



[a] Reaction conditions: *rac*-**2** (0.15–0.25 mmol), $SiCl_4$ (0.5–1.2 equiv), $R^3CHO$ (1.3 equiv), $CH_2Cl_2$ (3–5 mL), −78 °C–−60 °C, 2–8 h. [b] Yield of isolated product based on the recovered starting material. The conversions of *rac*-**2** were generally over 90%. [c] The diastereoselectivity (*ds*) was determined by $^1H$ NMR spectroscopy. [d] Desilylation product (*rac*-**4r**) was isolated in 12% yield. [e] The conversion of *rac*-**2t** was 78% when 0.3 equiv of $SiCl_4$ was used.




***Scheme 2.*** Rearrangement of racemic stereoisomers of 1,3-diol (*rac*-**2**).

The efficacy of the rearrangement may be determined by two scenarios: 1) the stereochemically defining step is controlled by a six-membered chairlike transition conformation; 2) other diastereoisomers (such as *anti*,*syn*-**2a** and *syn*,*anti*-**2q**[10] in Scheme 2) generated in the allylboration step were inactive to the oxonia-Cope rearrangement under the standard reaction conditions. The major stereoisomer *syn*,*syn*-**2** adopts a chairlike transition state whereas $R^3$ and bulky $R^1$/OTBS groups are equatorial after the formation of oxonium intermediate **A** in the presence of a Lewis acid, and subsequently collapses to form (*E*)-1,5-*anti*-**3** (Scheme 3). In

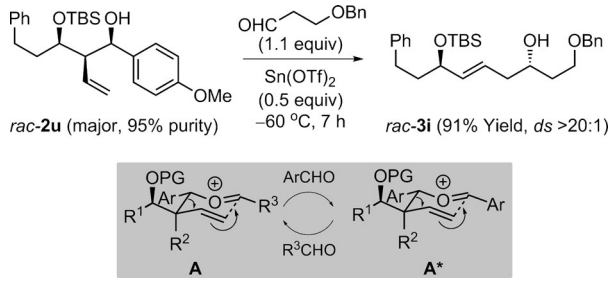



***Scheme 3.*** Mechanistic rationale of oxonia-Cope rearrangement. LA = Lewis acid.

contrast to intermediate **A**, the *syn* pentane interaction[13] anticipated between $R^3$ and OTBS groups in conformation **B** and the $R^3$/$R^1$ groups in conformation **C** would enhance the energy barrier for the rearrangement of *syn*,*anti*-**2** and *anti*,*syn*-**2**, respectively. In the favorable intermediate **A**, methyl, ethyl, and cyclopropane groups ($R^2$ in Scheme 3) here are well tolerated and the desired products were achieved with good 1,5-steoreocontrol. However, the phenyl group residing at the $R^1$ position in **2l** might destabilize the oxonium intermediate to retard the subsequent rearrangement, while the substrate **2f** remains effective to afford **3f** in excellent yield.

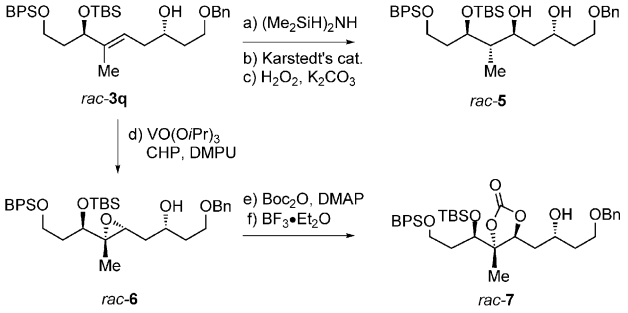
The dual function of the aldehyde $R^3CHO$ involved in the preparation of the 1,3-diols (**2**) and subsequent rearrangement may restrict the applications because of the limited availability of highly functionalized aldehyde. The promiscuity of the rearrangement reaction for different aldehydes makes selective replacement of the first aldehyde by a second aldehyde challenging. Our preliminary efforts (see Table S3 in the Supporting Information) identified *p*-anisaldehyde as a surrogate in the cascade hydroboration/allylation process and the corresponding racemic *syn*,*syn*-1,3-diol **2u** was isolated in 88% yield (major, 95% purity). In the presence of $Sn(OTf)_2$, the rearrangement occurred smoothly with 1.1 equivalents of external 3-benzyloxypropanal at −60 °C to deliver 1,5-*anti*-**3i** in 91% yield upon isolation (*ds* > 20:1; Scheme 4). As depicted in the chairlike oxonium intermediates **A** and **A***, the conjugation by aromatic rings in **A*** is assumed to retard the subsequent Prins-type cyclization and fragmentation.

The corresponding 1,5-pentendiols can be readily converted into versatile polyol building blocks. It is known from the work of the group of Roush[14] that the *syn* selectivity of hydrosilylation was proposed to go through a chairlike




***Scheme 4.*** Oxonia-Cope rearrangement of cross-aldehyde.

transition state with a pseudoequatorial olefin group. Interestingly, the opposite *trans* selectivity (*ds* 20:1) was obtained with the 1,5-pentenediol **3q** (Scheme 5). Subsequent oxida-




***Scheme 5.*** Synthesis of polyol: a) $(Me_2SiH)_2NH$ (2.5 equiv), RT; b) Karstedt's catalyst (0.5 mol%), toluene; c) $H_2O_2$ (2.5 equiv), $K_2CO_3$, MeOH/THF (1:1), 62% for 3 steps (brsm, unoptimized); d) $VO(OiPr)_3$ (10 mol%), CHP (1.5 equiv), DMPU, 4 Å M.S., RT, 24 h, 89% (*ds* 20:1); e) DMAP, $Boc_2O$, THF, 98% brsm; f) $BF_3{\cdot}Et_2O$ (1.5 equiv), $CH_2Cl_2$, 95%. $Boc_2O$ = di-*tert*-butyl dicarbonate, CHP = cumene hydroperoxide, DMAP = 4-dimethylaminopyridine, DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone, M.S. = molecular sieves, THF = tetrahydrofuran.

tive hydrolysis delivered the skipped *syn*,*anti*-triol **5** in 62% overall yield by a three-step sequence. Moreover, a vanadium-complex-catalyzed epoxidation was guided by the homoallylic alcohol in **3q** to afford **6** with an excellent diastereomeric ratio (β:α, 20:1).[15] The secondary alcohol (5-OH) was then protected with the Boc group and the corresponding epoxycarbonate underwent oxacyclization[16] in the presence of $BF_3{\cdot}Et_2O$ to give the 1,3-dioxolanone **7** in excellent yield.

In summary, a non-aldol approach featuring an oxonia-Cope rearrangement delivers 1,5-pentendiols and 2-alkyl-1,5-pentendiols with a uniformly high level of diastereoselectivity without resorting to stoichiometric use of chiral auxiliaries and chiral borane reagents. The origin of stereospecific chiral transfer is attributed to the chairlike anti-conformation of the oxonium ion intermediate (**A** in Scheme 3). The $SiCl_4$-promoted diastereomer-discriminating step is also noteworthy since other diastereomers provided by the allylboration were inert to the subsequent rearrangement and thus obliterates the contamination of *syn*-1,5-diol. Moreover, $Sn(OTf)_2$-catalyzed cross-aldehyde in the rearrangement greatly broadens its capacity of functionalized alkyl aldehydes. The strategic manipulation of the alkene into a polyhydroxylated moiety in a stereodefined manner demonstrated its potential to access polyol-embedded structures.

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