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Et_3B-mediated two- and three-component coupling reactions *via* radical decarbonylation of α-alkoxyacyl tellurides: single-step construction of densely oxygenated carboskeletons†

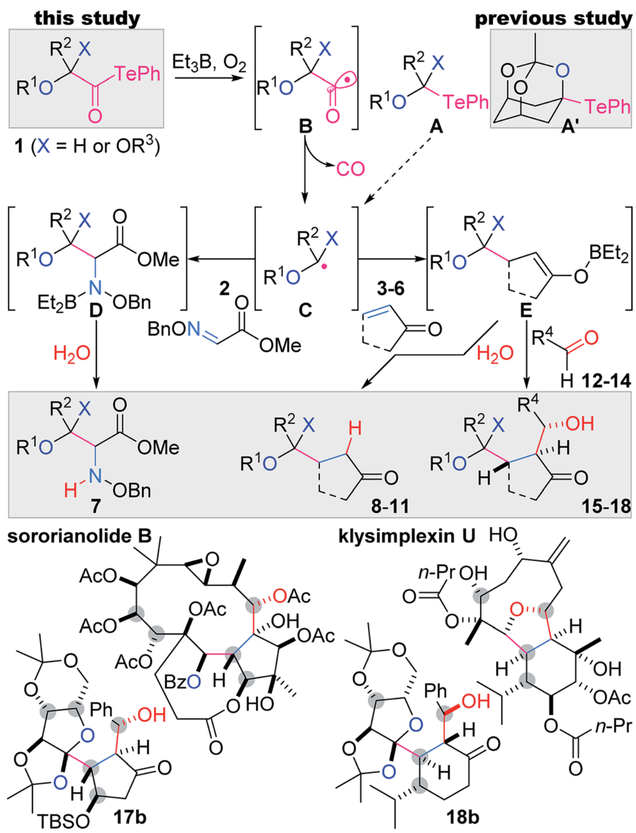
Masanori Nagatomo, Daigo Kamimura, Yuki Matsui, Keisuke Masuda and Masayuki Inoue*

The single-step construction of various densely oxygenated carboskeletons was achieved by radical-based two- and three-component coupling reactions of sugar derivatives, without the need for light or heat. Et_3B/O_2-mediated decarbonylation readily converted α-alkoxyacyl tellurides to α-alkoxy carbon radicals, which intermolecularly added to glyoxylic oxime ether or enones to provide the two-component adducts. Furthermore, the three-component adducts were produced by an intermolecular aldol reaction between the aldehyde and the boron enolates generated by capture of the two-component radical intermediates by Et_3B. This powerful coupling method serves as a novel strategy for the convergent synthesis of polyol natural products.

Introduction

Contiguously substituted polyol structures are found not only in numerous saccharides, but also in diverse secondary metabolites. For example, highly oxygenated terpenoids often accommodate such substructures (*e.g.*, sororianolide B,[1] klysimplexin U,[2] Scheme 1). As the oxygen-based functional groups potentially form hydrogen bonds with biological polymers, polyol natural products often exhibit potent bioactivities. Therefore, these complex terpenoids are expected to function as selective cellular probes and pharmacologically useful compounds.

The presence of a greater number of oxygen-attached stereocenters with increased density in bioactive polyol natural products heightens the challenge of their chemical synthesis.[3] In designing shorter and simpler synthetic routes to these complex targets, the convergent assembly of oxygenated fragments is most desirable, as this would minimize post-coupling manipulations of the functional groups. Radical-based reactions enable the highly chemoselective formation of carbon–carbon (C–C) bonds without affecting most oxygen-based functional groups and thus are particularly suitable as powerful convergent methodologies.[4] Here we report mild and robust two- and three-component radical coupling reactions using multiply oxygenated α-alkoxyacyl tellurides **1** and Et_3B as the key reagents. The versatility of this process was demonstrated

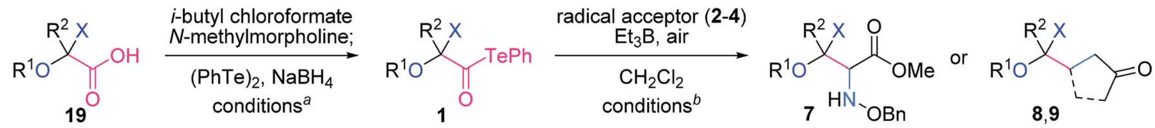


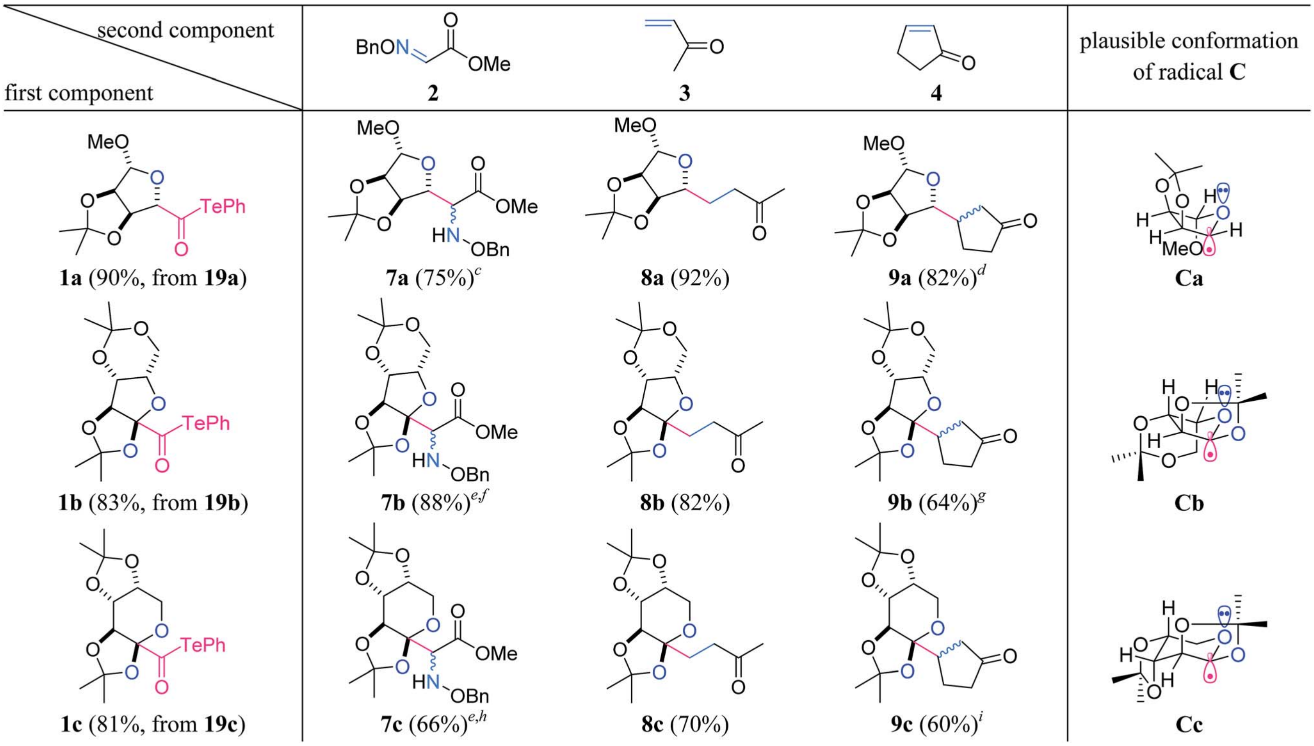
Scheme 1 The present two- and three-component coupling reactions *via* radical decarbonylation of α-alkoxyacyl tellurides, and representative polyol natural products.

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. E-mail: inoue@mol.f.u-tokyo.ac.jp

† Electronic supplementary information (ESI) available: Experimental protocols, characterization data, and NMR spectra of all new compounds. See DOI: 10.1039/c5sc00457h

Table 1 Preparation of α-alkoxyacyl tellurides and their reactions with glyoxylic oxime ether and enones





[a] Reagents and conditions: **19** (1 equiv.), i-butyl chloroformate (1.2 equiv.), *N*-methylmorpholine (1.2 equiv.), THF (0.2 M), 0 °C, 30 min; $(PhTe)_2$ (1 equiv.), $NaBH_4$ (3 equiv.), THF/MeOH (10 : 1, 0.2 M), 0 °C, 30 min; rt, 30 min. [b] **1** (1 equiv.), **2–4** (2 equiv.), Et_3B (3 equiv.), CH_2Cl_2 (0.02 M), rt, under air. [c] dr = 2 : 1. [d] dr = 3 : 1. [e] The reaction was carried out in CH_2Cl_2 (0.1 M). [f] dr = 1 : 1. [g] dr = 1.3 : 1. [h] dr = 1.5 : 1. [i] dr = 1.4 : 1.

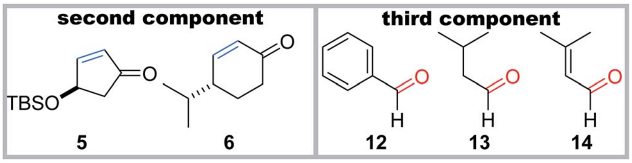
by the single-step preparation of variously adorned structures (**7–11**, **15–18**), including the polyol fragments of sororianolide B (**17b**) and klysimplexin U (**18b**).

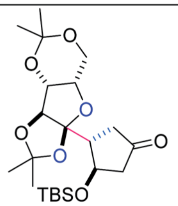
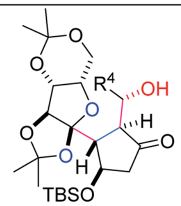
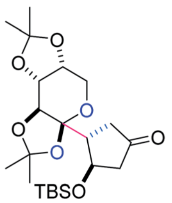
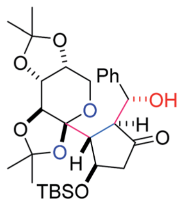
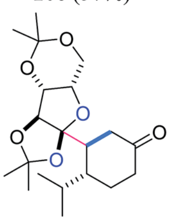
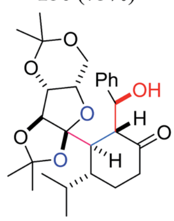
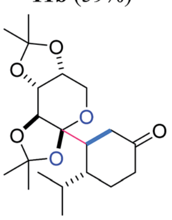
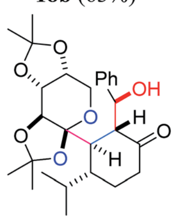
Results and discussion

We recently demonstrated facile bridgehead radical formation from a mono-telluro acetal **A′** by the action of Et_3B and O_2 (Scheme 1).[5,6] However, expansion of the substrate scope of this reaction was unsuccessful because of the chemical instability of the mono-telluro acetal (X = H) and the orthoester **A** (X = OR^3).[7] Thus, the C–Te bond of **A** typically undergoes heterolytic cleavage by electron donation from the oxygen lone pair, while such electron donation is uniquely impeded in **A′** due to the anti-Bredt character of the resultant oxocarbenium ion. In this context, we alternatively designed more stable α-alkoxyacyl tellurides **1** as precursors to α-alkoxy radical intermediates **C**.[8] An Et radical generated from Et_3B/O_2 [9] would induce the C–Te homolysis of **1**, leading to the acyl radical **B**, the decarbonylation of which would give rise to the requisite radical **C**.[10,11] According to our presumed scenario, the nucleophilic radical **C** would then react intermolecularly with the electrophilic C=N bond of **2** and the C=C bond of **3–6** to generate the corresponding N- and C-radicals, respectively. Et_3B in turn would transform these radicals into the polar intermediates **D** and **E** through ejection of an Et radical,[12] and subsequent protonation would afford the two-component adducts **7** and **8–11**, respectively. The boron enolate **E** would further react with aldehydes **12–14** *via* the aldol reaction, resulting in the formation of the three-component products **15–18**. Most importantly, this intricate yet attractive plan would be realized only when all of the reactants properly follow the series of depicted radical and polar reactions in a single flask.

β-D-Ribofuranosiduronic acid derivative **19a**, 2-keto-L-gulonic acid derivative **19b**, and β-D-arabino-2-hexulopyranosonic acid derivative **19c** were selected as readily available carboxylic acids with four contiguous oxygen-attached stereocenters (Table 1). α-Alkoxyacyl tellurides **1a–c** were then obtained from the sugar-derived acids **19a–c** in one pot. Namely, **19** was first transformed into the activated ester *via* condensation with i-butyl chloroformate, and was then treated *in situ* with PhTeNa, prepared from $(PhTe)_2$ and $NaBH_4$, providing **1**. The structurally distinct

Table 2 Stereoselective two and three-component coupling reactions



	third component	
	none	R^4CHO (**12-14**)
1b+5	 **10b** (65%)[a]	 **15b**: R^4 = Ph (88%)[c] **16b**: R^4 = *i*-Bu (85%)[c] **17b**: R^4 = CH=CMe$_2$ (79%)[c]
1c+5	 **10c** (57%)[a]	 **15c** (73%)[c]
1b+6	 **11b** (59%)[b]	 **18b** (63%)[d]
1c+6	 **11c** (56%)[b]	 **18c** (46%)[d]

[a] Reagents and conditions: **1b,c** (1 equiv.), **5** (2 equiv.), Et_3B (3 equiv.), CH_2Cl_2 (0.02 M), rt, under air. [b] **1b,c** (1 equiv.), **6** (5 equiv.), Et_3B (3 equiv.), CH_2Cl_2 (0.1 M), rt, under air. [c] **1b,c** (1 equiv.), **5** (2 equiv.), **12–14** (3 equiv.), Et_3B (3 equiv.), CH_2Cl_2 (0.1 M), rt, under air. [d] **1b,c** (1 equiv.), **6** (3 equiv.), **12** (5 equiv.), Et_3B (3 equiv.), CH_2Cl_2 (0.1 M), rt, under air.

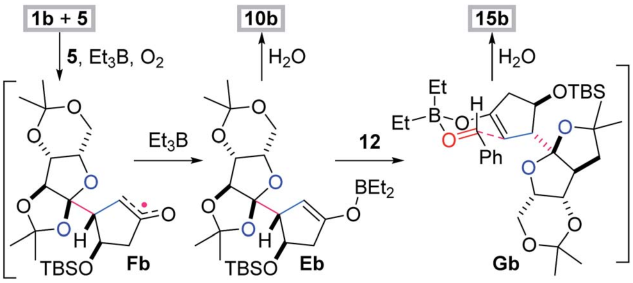
alkoxyacyl tellurides **1a–c** were found to be stable to air, light and silica gel.

Significantly, the two-component radical reactions between the three radical donors **1a–c** and three radical acceptors **2–4** all efficiently proceeded to generate nine complex adducts (Table 1).[13,14] In these reactions, α-alkoxyacyl telluride (**1a**, **b** or **c**) was simply treated with 2 equiv. of the acceptor (**2**, **3** or **4**) and 3 equiv. of Et_3B under air in CH_2Cl_2 at room temperature.[15] As a result, three highly oxygenated α-amino acid derivatives **7a–c** were directly constructed using the *O*-benzyl-protected methyl glyoxylate oxime **2** as the acceptor.[16] An alternative application for α,β-unsaturated ketones **3** and **4** permitted the attachment to the linear carboskeleton of **8a–c** and the branched carboskeleton of **9a–c**, respectively. The absence of the formation of any potential by-products derived from the addition of the acyl radicals proved that radical decarbonylation consistently occurred prior to the intermolecular addition to the C=N or C=C bond. C–C homolysis of the acyl radicals is likely facilitated by the stabilizing orbital interaction between the alkyl radical and the adjacent oxygen lone pair in **Ca–c**.[17]

The resultant compounds **Ca–c** exhibited potent reactivity as nucleophilic radicals, and stereoselectively constructed the trisubstituted (**7a–9a**) and tetrasubstituted carbons (**7b–9b**, **7c–9c**) on the ether rings (Table 1). The observed stereochemical outcome could be explained by a combination of stereoelectronic and steric effects. The three-dimensional structures of **Ca–c** represent their assumed conformations, where the interaction of the σ-radical orbital and the non-bonding O-electron pair increase both the stability and nucleophilicity of the axial σ-radical.[18,19] The approach of the acceptor only occurs from the α-face of the molecule because of the concave nature of the β-face.[20] In the case of **7b–9b** and **7c–9c**, the favorable formation of the *cis*-fused bicycle in comparison to the strained *trans*-fused counterpart contributes to the excellent stereoselectivity at the ring junction.[21] Overall, the results in Table 1 proved the high utility of the contiguously substituted polyol radical donors **1a–c**.

Although the stereoselectivity at the radical accepting position in **7a–c** and **9a–c** was not high (dr = 3 : 1–1 : 1), the pre-existing stereocenters of acceptors **5** and **6** perfectly governed the stereochemical outcome of the two-component reactions (Table 2). Specifically, the β-oriented TBS-oxy group of **5** induced the selective α-face addition of the radical that was generated from **1b** or **1c** in the presence of Et_3B/O_2, giving rise to **10b** or **10c** as the sole stereoisomer. On the other hand, the radical addition to **6** occurred trans to its α-configured isopropyl group, predominantly leading to **11b** or **11c**.

Furthermore, the three-component coupling reactions were realized with complete control of the four stereocenters (Table 2). When a mixture of acyl telluride **1b**, **5** (2 equiv.) and benzaldehyde **12** (3 equiv.) was treated with Et_3B/O_2 at room temperature, only **15b** was obtained in a high yield. The aliphatic aldehyde **13** and the even α,β-unsaturated aldehyde **14** also served as the third components without decreasing the yields to afford **16b** and **17b**, respectively. Application of the different radical donor **1c** with **5** and **12** also resulted in the smooth formation of the adduct **15c**. The 6-membered enone **6** participated in the three-component reactions upon use of **1b** and **1c** in the presence of **12**, delivering **18b** and **18c**, respectively. It is noteworthy that the one-step construction of the complex products with eight contiguous stereocenters was achieved under neutral conditions, and the five stereocenters of **15b–17b** and the four stereocenters of **18b** directly matched



Scheme 2 Rationale of the stereochemical outcome.

those of sororianolide B and klysimplexin U, respectively (highlighted as gray circles in Scheme 1). These data together proved the power of the present convergent methodology for the synthesis of densely oxidized carboskeletons.

The radical-polar crossover mechanism of the two- and three-component reactions was exemplified by the synthesis of **10b** and **15b** (Scheme 2).[22] The Et_3B-mediated radical reaction between **1b** and **5** stereoselectively generates the radical intermediate **Fb**,[23] which is transformed to the boron enolate **Eb** by capture with Et_3B. Protonation of the polar intermediate **Eb** affords the two-component adduct **10b**. Alternatively, aldehyde **12** approaches **Eb** from the face opposite to the bulky fused tricycle and forms the chair-like six-membered transition state **Gb**,[24] subsequently establishing the stereocenters of the α- and β-positions of the ketone of **15b**. Three of the four newly introduced stereocenters of **15–17** and **18** are opposite because the configuration of the isopropyl group of **6** is the inverse of the TBS-oxy group of **5** (Table 2). Hence the stereochemical consistency in both the radical and aldol reactions is one of the most remarkable features of the present methodology.

Conclusions

In summary, we devised new radical-based two- and three-component coupling reactions, and realized the one-step construction of contiguously substituted polyol structures, which are significantly difficult to access by other methods. Upon activation with Et_3B/O_2, α-alkoxyacyl tellurides were rapidly converted to α-alkoxy radicals through expulsion of CO, thereby serving as the surrogate of the unstable mono-telluro acetals or orthoesters. Despite the sterically hindered nature, the resultant secondary or tertiary radical possessed potent reactivity toward the oxime and enone to stereoselectively furnish a variety of two-component adducts. Furthermore, the boron enolate, the intermediate in the two-component reaction, effectively participated in the aldol reaction with the third component, leading to another series of products. The three component coupling reactions simultaneously installed four contiguous stereocenters, and thus are particularly useful in increasing the complexity of the molecule in a single step. Because of the simplicity of the reagent system and the mildness of the conditions, this powerful radical technology introduces a novel convergent strategy for the expedited total synthesis of densely oxidized natural products.

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