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Et₃B-mediated two- and three-component coupling reactions *via* radical decarbonylation of α -alkoxyacyl tellurides: single-step construction of densely oxygenated carboskeletons†

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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. Et₃B/O₂-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 Et₃B. This powerful coupling method serves as a novel strategy for the convergent synthesis of polyol natural products.

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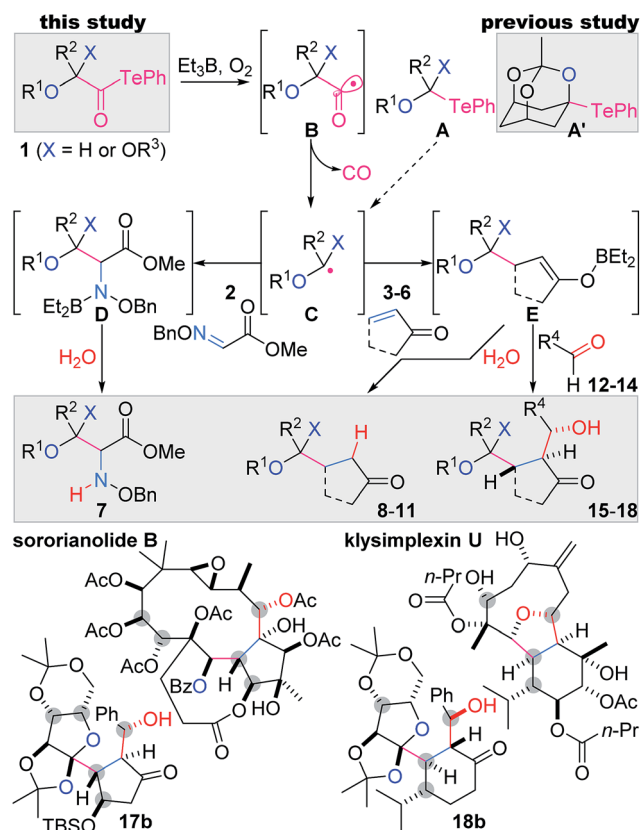
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Introduction

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 Et₃B 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.

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

second component				plausible conformation of radical C
first component	2	3	4	
1a (90%, from 19a)	7a (75%) ^c	8a (92%)	9a (82%) ^d	Ca
1b (83%, from 19b)	7b (88%) ^{e,f}	8b (82%)	9b (64%) ^g	Cb
1c (81%, from 19c)	7c (66%) ^{e,h}	8c (70%)	9c (60%) ⁱ	Cc

^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.), NaBH₄ (3 equiv.), THF/MeOH (10 : 1, 0.2 M), 0 °C, 30 min; rt, 30 min. ^b **1** (1 equiv.), **2-4** (2 equiv.), Et₃B (3 equiv.), CH₂Cl₂ (0.02 M), rt, under air. ^c dr = 2 : 1. ^d dr = 3 : 1. ^e The reaction was carried out in CH₂Cl₂ (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 Et₃B and O₂ (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 = OR³).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 Et₃B/O₂⁹ 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. Et₃B 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 NaBH₄, providing **1**. The structurally distinct



Table 2 Stereoselective two and three-component coupling reactions

	second component		third component	
	5	6	12	13
			third component	
			none	R ⁴ CHO (12-14)
1b+5				
	10b (65%) ^a			15b: R ⁴ = Ph (88%) ^c 16b: R ⁴ = <i>i</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.), Et₃B (3 equiv.), CH₂Cl₂ (0.02 M), rt, under air. ^b **1b,c** (1 equiv.), **6** (5 equiv.), Et₃B (3 equiv.), CH₂Cl₂ (0.1 M), rt, under air. ^c **1b,c** (1 equiv.), **5** (2 equiv.), **12-14** (3 equiv.), Et₃B (3 equiv.), CH₂Cl₂ (0.1 M), rt, under air. ^d **1b,c** (1 equiv.), **6** (3 equiv.), **12** (5 equiv.), Et₃B (3 equiv.), CH₂Cl₂ (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

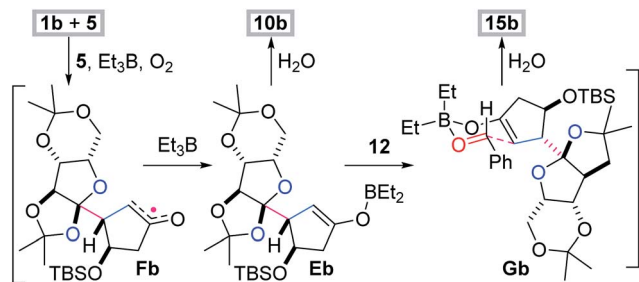
simply treated with 2 equiv. of the acceptor (**2, 3** or **4**) and 3 equiv. of Et₃B under air in CH₂Cl₂ at room temperature.¹⁵ As a result, three highly oxygenated α -amino acid derivatives **7a-c** were directly constructed using the *O*-benzyl-protected methyl glyoxylate oxime **2** as the acceptor.¹⁶ 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 stereo-electronic 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 Et₃B/O₂, 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 Et₃B/O₂ 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 Et₃B-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 Et₃B. 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 tricyclic 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 Et₃B/O₂, 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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Notes and references

- 1 Y. Huang and H. A. Aisa, *Helv. Chim. Acta*, 2010, **93**, 1156.
- 2 B.-W. Chen, C.-Y. Huang, Z.-H. Wen, J.-H. Su, W.-H. Wang, P.-J. Sung, Y.-C. Wu and J.-H. Sheu, *Bull. Chem. Soc. Jpn.*, 2011, **84**, 1237.
- 3 For selected reviews on the total synthesis of terpenoids, see: (a) K. C. Nicolaou, D. Vourloumis, N. Winssinger and P. S. Baran, *Angew. Chem., Int. Ed.*, 2000, **39**, 44; (b) T. J. Maimone and P. S. Baran, *Nat. Chem. Biol.*, 2007, **3**, 396; (c) E. C. Cherney and P. S. Baran, *Isr. J. Chem.*, 2011, **51**, 391.
- 4 For recent reviews on radical reactions, see: (a) G. S. C. Srikanth and S. L. Castle, *Tetrahedron*, 2005, **61**, 10377; (b) G. J. Rowlands, *Tetrahedron*, 2009, **65**, 8603; (c) G. J. Rowlands, *Tetrahedron*, 2010, **66**, 1593.
- 5 D. Kamimura, D. Urabe, M. Nagatomo and M. Inoue, *Org. Lett.*, 2013, **15**, 5122.
- 6 For reviews on the radical reactions of organotellurides, see: (a) S. Yamago, *Synlett*, 2004, 1875; (b) N. Petraghani and H. A. Stefani, *Tellurium in Organic Synthesis*, Elsevier, New York, 2nd edn, 2007.
- 7 Although mono-telluro acetals have been utilized as radical donors, the synthesis of a mono-telluro orthoester has not been reported. (a) D. H. R. Barton and M. Ramesh, *J. Am. Chem. Soc.*, 1990, **112**, 891; (b) W. He, H. Togo, Y. Waki and M. Yokoyama, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2425; (c) S. Yamago, H. Miyazoe and J. Yoshida, *Tetrahedron Lett.*, 1999, **40**, 2343; (d) H. Miyazoe, S. Yamago and J. Yoshida, *Angew. Chem., Int. Ed.*, 2000, **39**, 3669; (e) S. Yamago, H. Miyazoe, R. Goto, M. Hashidume, T. Sawazaki and J. Yoshida, *J. Am. Chem. Soc.*, 2001, **123**, 3697; (f) S. Yamago, M. Miyoshi, H. Miyazoe and J. Yoshida, *Angew. Chem., Int. Ed.*, 2002, **41**, 1407.
- 8 Most recently, we developed decarbonylative two-component coupling reactions of α -aminoacyl tellurides. M. Nagatomo, H. Nishiyama, H. Fujino and M. Inoue, *Angew. Chem., Int. Ed.*, 2015, **54**, 1537.
- 9 K. Nozaki, K. Oshima and K. Utimoto, *J. Am. Chem. Soc.*, 1987, **109**, 2547. For a review, see: C. Ollivier and P. Renaud, *Chem. Rev.*, 2001, **101**, 3415.
- 10 For a review on acyl radical reactions and decarbonylation rates, see: (a) D. L. Boger, *Isr. J. Chem.*, 1997, **37**, 119; (b) C. Chatgililoglu, D. Crich, M. Komatsu and I. Ryu, *Chem. Rev.*, 1999, **99**, 1991.
- 11 For selected examples of recent decarboxylative (–CO₂) two-component radical coupling, see: (a) Y. Yoshimi, K. Kobayashi, H. Kamakura, K. Nishikawa, Y. Haga, K. Maeda, T. Morita, T. Itou, Y. Okada and M. Hatanaka, *Tetrahedron Lett.*, 2010, **51**, 2332; (b) M. J. Schnermann and L. E. Overman, *Angew. Chem., Int. Ed.*, 2012, **51**, 9576; (c)



- L. Chu, C. Ohta, Z. Zuo and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2014, **136**, 10886.
- 12 (a) N. Miyaura, M. Harada, M. Itoh and A. Suzuki, *Chem. Lett.*, 1973, 1145; (b) K. Nozaki, K. Oshima and K. Utimoto, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 403.
- 13 The stereochemistries of the newly synthesized compounds were established from NMR experiments on derivatized compounds. See ESI† for details.
- 14 We confirmed from a separate experiment that the selenide version of **1a** was inert toward our reagent system (Et₃B/O₂/rt), corroborating the superior reactivity of the acyl telluride in comparison to the acyl selenide. See also ref. 5.
- 15 Acyl tellurides were previously converted to the acyl radicals either by thermolysis (>100 °C) or UV photolysis. (a) C. Chen, D. Crich and A. Papadatos, *J. Am. Chem. Soc.*, 1992, **114**, 8313; (b) D. Crich, C. Chen, J.-T. Hwang, H. Yuan, A. Papadatos and R. I. Walter, *J. Am. Chem. Soc.*, 1994, **116**, 8937; (c) B. D. Horning and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2013, **135**, 6442, See also ref. 7e.
- 16 (a) H. Miyabe, C. Ushiro, M. Ueda, K. Yamakawa and T. Naito, *J. Org. Chem.*, 2000, **65**, 176; (b) H. Miyabe, *Synlett*, 2012, **23**, 1709.
- 17 Stabilization of the alkyl radical was known to accelerate decarbonylation of the acyl radical. (a) H. Fischer and H. Paul, *Acc. Chem. Res.*, 1987, **20**, 200; (b) D. L. Boger and R. J. Mathvink, *J. Org. Chem.*, 1992, **57**, 1429. See also ref. 10.
- 18 Interaction between the singly occupied orbital and the σ* orbital of the coplanar β-C-OR bond could further stabilize the radical. For structures of α-alkoxy radicals, see: (a) B. Giese and J. Dupuis, *Tetrahedron Lett.*, 1984, **25**, 1349; (b) A. L. J. Beckwith and P. J. Duggan, *Tetrahedron*, 1998, **54**, 6919; (c) S. D. Rychnovsky, J. P. Powers and T. J. LePage, *J. Am. Chem. Soc.*, 1992, **114**, 8375; (d) H. Abe, S. Shuto and A. Matsuda, *J. Am. Chem. Soc.*, 2001, **123**, 11870, For reviews, see: (e) J.-P. Praly, *Adv. Carbohydr. Chem. Biochem.*, 2000, **56**, 65.
- 19 For reviews on stereoselectivity on reactions of α-alkoxy radicals, see: (a) B. Giese, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 969; (b) H. Togo, W. He, Y. Waki and M. Yokoyama, *Synlett*, 1998, 700.
- 20 (a) D. H. R. Barton, S. D. Géro, B. Quiclet-Sire and M. Samadi, *J. Chem. Soc., Chem. Commun.*, 1988, 1372; (b) E. Vismara, G. Torri, N. Pastori and M. Marchiandi, *Tetrahedron Lett.*, 1992, **33**, 7575; (c) D. H. R. Barton, S. D. Géro, B. Quiclet-Sire and M. Samadi, *Tetrahedron: Asymmetry*, 1994, **5**, 2123.
- 21 D. Crich and L. B. L. Lim, *J. Chem. Soc., Perkin Trans. 1*, 1991, 2209.
- 22 For reviews on the radical-polar crossover reactions, see: (a) J. A. Murphy, *The Radical-Polar Crossover Reaction*, in *Radicals in Organic Synthesis*, ed. P. Renaud and M. P. Sibi, Wiley-VCH, Weinheim, 2001, vol. 1, pp. 298–315; (b) I. Ryu, *Chem. Rec.*, 2002, **2**, 249; (c) E. Godineau and Y. Landais, *Chem.–Eur. J.*, 2009, **15**, 3044.
- 23 Formation of PhTeEt was observed.
- 24 (a) W. Fenzl and R. Köster, *Liebigs Ann. Chem.*, 1975, 1322; (b) T. Inoue and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 174; (c) D. A. Evans, J. V. Nelson, E. Vogel and T. R. Taber, *J. Am. Chem. Soc.*, 1981, **103**, 3099.

