/ Review

Radical-Mediated Three-Component Reaction: A Study toward the Total Synthesis of Resiniferatoxin

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This review summarizes the efforts to develop a radical-mediated three-component reaction and its application to a convergent approach to synthesize the 5/7/6-tricyclic framework (ABC-rings) of the densely functionalized daphnane diterpene, resiniferatoxin. The α -alkoxy bridgehead radical species, which was designed as the radical donor of the three-component reaction, was generated from O,Se- and O,Te-acetals under two different conditions. The generated α -alkoxy bridgehead radical effectively underwent the three-component reaction with α,β -unsaturated ketones and allyltributyltin/aldehyde under each of the conditions, giving rise to a wide variety of multiply functionalized 2,3-*trans* disubstituted cyclopentenone moieties. One of the established reactions was utilized as the key assembling reaction of the ABC-tricyclic framework of resiniferatoxin. The reaction of the bridgehead radical of the highly functionalized 6-membered C-ring, the 5-membered A-ring, and an allyltributyltin derivative effectively produced the C4-branched AC-rings. The last B-ring was constructed from the coupling adduct in two steps through the 7-*endo* cyclization, delivering the tricyclic framework possessing the correct C8 and 9-stereocenters of resiniferatoxin. The present methods demonstrate the power of the three-component reaction using an α -alkoxy bridgehead radical in a convergent approach to the complex architectures of daphnane diterpenes.

Key words total synthesis; diterpene; radical reaction; three-component reaction; stereoselective reaction

1. Introduction

The plant families Euphorbiaceae and Thymelaeaceae are rich sources of bioactive diterpenes.^{1–3} Daphnane is a major class of diterpenes and has received considerable attention due to its important pharmacological activity.^{4–6} Resiniferatoxin (**1**, Fig. 1), a representative daphnane diterpene, is the irritant in the latex of *Euphorbia resinifera*.^{7,8} A detailed biological study revealed that **1** is a potent activator of the ion channel, transient receptor potential vanilloid 1, in the plasma membrane of sensory neurons.^{9,10} The strong analgesic property of **1** caused by desensitization of nociceptive neurons offers **1** as a potential therapeutic agent. Two other daphnanes, daphnetoxin^{11,12} and trigohownin A,¹³ have more highly oxidized carbon frameworks and a phenyl orthoester and display different bio-functions: daphnetoxin is a human immunodeficiency virus (HIV) inhibitor while trigohownin A exhibits cytotoxic activity. The broad spectrum of bioactivity exhibited by daphnanes is attributed to the diverse pattern of oxygen functional groups on the *trans*-fused 5/7/6-membered tricyclic framework (ABC-rings) and two types of orthoester (C9,13,14- or C9,12,14-orthoester) decorated with a variety of substituents.

The beneficial pharmacological effects coupled with the intriguingly complex architectures of daphnanes have spurred intense interest in the chemical community.^{14,15} From a synthetic standpoint, the ABC-tricyclic system comprising a number of contiguous stereocenters and the extraordinary orthoesters^{8,16,17} are appealing for devising synthetic strate-

gies. However, the successful total synthesis of daphnanes has been limited to reports from Wender's group,^{18,19} despite extensive synthetic efforts by other research groups.^{20–36} We also have been inspired by the formidable structures of daphnanes to launch a synthetic study of **1** as the initial target. This review summarizes our effort to develop a key radical-mediated three-component reaction and its application to the convergent assembly of the tricyclic ABC-ring system of **1**.

2. Radical-Mediated Three-Component Reaction^{37–39}

The over 120 species of daphnane diterpenes in nature provided us insights into employing a convergent strategy toward the total synthesis of resiniferatoxin (**1**). In general, a convergent approach to a target natural product is advantageous compared to a linear approach in the sense that the number of linear steps from a starting material to the natural product is minimized, and the diverse structures of the target natural product are accessible by coupling differently functionalized fragments.⁴⁰ Accordingly, the incorporation of functionalized fragments into the ABC-tricyclic framework of **1** would be an expedient approach to the unified total synthesis of daphnanes. However, there are few C–C bond forming reactions that do not harm labile functional groups. From this perspective, development of a powerful and reliable methodology for fragment coupling was the initial challenge.

We focused on a coupling method comprising the three-component reaction of an α -alkoxy bridgehead radical species,

Fig. 1. Structures of Daphnane Diterpenes

cyclic α,β -unsaturated ketone, and allyltributyltin/aldehyde. The advantage of a radical-mediated C–C bond formation for fragment coupling is the high reactivity of the radical species, enabling the formation of congested C–C bonds, and orthogonality to polar functional groups.^{41–43)} In addition, an α -alkoxy bridgehead radical is spatially exposed and thus reactive, and the stereocenter is fixed by the cage structure throughout the reaction.^{44–52)} We postulated that a three-component reaction using an α -alkoxy bridgehead radical species would allow convergent assembly of the multiply oxygenated polycyclic structure of **1**.^{53,54)}

Our study started with the synthesis of two precursors of the α -alkoxy bridgehead radical species and investigation of the reactivity of the radical using a simple orthoester model of resiniferatoxin (**1**, Chart 1). Condensation of carboxylic acid **2** with 2-mercaptopyridine *N*-oxide **3** using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI) yielded Barton ester **4**,^{55–57)} which was *in situ* photo-irradiated with (PhSe)₂ and (PhTe)₂ to afford O,Se- and O,Te-acetals **5a**, respectively. Treatment of **5a** with V-40 (0.4 eq) and *n*-Bu₃SnH (6 eq) in refluxing toluene induced homolytic cleavage of the C–Se bond to generate α -alkoxy bridgehead radical **7**. The radical **7** underwent coupling with cyclopentenone **6a** (5 eq), producing adduct **8a** in 77% yield. The C–Se bond of **5a** was inert upon treatment with Et₃B (3 eq)/O₂ at 0°C,^{58,59)} and **5a** was quantitatively recovered. In contrast, the C–Te bond of **5b** was effectively cleaved using the above Et₃B/O₂ system to generate bridgehead radical **7**, which reacted with **6a** (3 eq) at 0°C to afford **8a** in 85% yield.^{60,61)} It is noteworthy that two different methods generated the same α -alkoxy bridgehead

Chart 1. Investigation of the Reactivity of the α -Alkoxy Bridgehead Radical under Two Distinct Conditions

radical species **7**, which linked the two oxygenated 5 and 6-membered carbocycles under each of the conditions to furnish **8a**.

The distinctive behavior between O,Se- and O,Te-acetals as radical donors led us to plan two types of three component reactions from orthoesters **5a** and **5b** (Chart 2A). Homolytic cleavage of the C–Se bond of **5a** with stannyl radical (Y=*n*-Bu₃Sn) would generate radical **7**, which was to react with cyclic α,β -unsaturated ketone **6**, resulting in the formation of 2,3-*trans*-disubstituted cyclic ketone **11** after introduction of the R¹ group of **10** to **9**. We anticipated that the nature of the radical species would define the multiple reaction process. Specifically, nucleophilic radical **7** assisted by the α -oxygen would preferentially react with the electron-deficient cyclic olefin of **6**. The generated electrophilic radical at the α -position of ketone **9** would capture the electron-rich tin reagent to form three-component adduct **11** and release stannyl radical, which should cleave the C–Se bond. Alternatively, ethyl radical (Y=Et), which is derived from Et₃B and O₂, can cleave the C–Te bond of **5b** to produce bridgehead radical **7**. After the addition of the bridgehead radical **7** to **6**, the resultant radical **9** was expected to be converted to anionic intermediate **12** in the presence of Et₃B.⁶²⁾ The crossover mechanism would lead to the next aldol reaction of the boron enolate **12** with aldehyde **13** to deliver 2,3-*trans*-disubstituted

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Chart 2. A: Three-Component Couplings *via* Radical/Radical (X=SePh, Y=*n*-Bu₃Sn) and Radical/Polar Cascade Reactions (X=TePh, Y=Et); B: Comparison of the Structures of Three-Component Adducts and Resiniferatoxin

cyclic ketone **14** with one more oxygen functional group than **11**.^{63–65} By applying these methods, we anticipated that the two different coupling products **11** and **14**, possessing AC-rings with the C9-tetra and C10-trisubstituted carbons of **1**, would be accessible (Chart 2B).

First, O,Se-acetal **5a** was subjected to the two-component reaction with cyclic α,β -unsaturated ketones to form linkages between two carbocyclic structures (Table 1). In the reactions, a syringe pump was used to slowly add *n*-Bu₃SnH (**10a**, 6eq) and V-40 (0.4eq) to the refluxing toluene solution and suppress the reduction of bridgehead radical **7** with excess *n*-Bu₃SnH. As with cyclopentenone **6a** in Chart 1, cyclohexenone **6b**, cycloheptenone **6c**, and cyclooctenone **6d** were attached to the bridgehead position to afford **8b**, **c**, and **d** in 56%, 26%, and 45% yields, respectively (entries 1–3). The reaction of **5a** with cyclopentenone **6e** possessing a *tert*-butyldimethylsilyl (TBS)-oxy group produced **8e** as a single diastereoisomer by addition from the opposite face of the functional group (entry 4).

The two-component radical reaction was extended to the three-component reaction (Table 2). Treatment of **5a** with cyclopentenone **6a**/cyclohexenone **6b**, allyltributyltin **10b**, and V-40 in toluene at 110°C produced 2,3-*trans*-disubstituted cycloalkane **11a/11b** as the single diastereomer (entries 1/2). In the coupling using **6e** as the radical acceptor, 2,3-*trans*-3,4-

Table 1. Two-Component Radical Reactions of O,Se-Acetal **5a** and **6**^{a)}

Entry	Radical acceptor	Product	Yield
1			56%
2			26%
3			45%
4			65% ^{b)}

^{a)} Reaction conditions: **5a** (1eq), **6** (5eq), **10a** (6eq), V-40 (0.4eq), toluene (0.02M), 110°C. **10a** and V-40 (0.2eq) were added by syringe pump over 3h, and the reaction mixture was stirred for an additional 1h. ^{b)} Compound **8e** was obtained as a single diastereoisomer.

trans-trisubstituted cyclopentanone **11c** was exclusively produced in 77% yield (entry 3).

The success of the three-component reaction using O,Se-acetal **5a** led us to turn to the other challenge of using O,Te-acetal **5b** (Table 3). The three-component reaction of O,Te-acetal **5b**, cyclopentenone **6a**, and aldehyde **13a/b/c** was initiated using the Et₃B/O₂ system at 0°C, producing **14a/b/c** as the sole stereoisomer (entries 1/2/3). Bulky aliphatic aldehydes **13d** and **e** were applicable to the coupling as trapping reagents for the boron enolate to afford **14d** and **e**, respectively (entries 4, 5). Although α,β -unsaturated aldehydes **13f** and **g** could potentially serve as acceptors of the bridgehead radical, the compounds were found to react as electrophiles with the boron enolate (entries 6, 7). Specifically, bridgehead radical **7** underwent the first radical addition to α,β -unsaturated ketone **6a** in the presence of **13f/g**, and the second aldol reaction occurred between the resultant boron enolate and the aldehyde, leading to the formation of **14f/g**. The scope of the coupling method was expanded to synthesize 2,3-*trans*-disubstituted cyclopentenones with a higher oxidation level. Specifically, cyclopentenones **6e** and **f** were utilized as the acceptors of bridgehead radical **7**, producing **14h** and **i**, respectively, after the aldol reaction with benzaldehyde **13a** (entries 8, 9). Importantly, all of the aldol reactions stereoselectively generated the configurations of the secondary hydroxy groups in **14**. The chair-like transition state **12'** can explain the stereoselective approach of the aldehydes to the enolates by avoiding the interaction with the bulky tri-oxadamantane orthoester^{66–70} (Fig. 2).

Table 2. Three-Component Radical Reactions of O,Se-Acetal **5a**, **6** and Allyltributyltin **10b**^{a)}

Entry	Radical acceptor	Allyltributyltin	Product	Yield ^{b)}
1				75%
2				32% ^{c)}
3				77%

a) Reaction conditions: **5a** (1 eq), **6** (5 eq), **10b** (6 eq), V-40 (0.4 eq), toluene (0.2 M), 110 °C, 8 h. b) Product was obtained as a single diastereoisomer. c) Compound **5a** was recovered in 15% yield.

3. Synthetic Study of Resiniferatoxin⁷¹⁾

We demonstrated that the radical-mediated three-component reactions effectively incorporated the two carbocycles and a carbon chain into the multiply functionalized compounds. Thus, we planned to integrate the three-component reaction as a key assembling reaction of the A- and C-rings of resiniferatoxin (**1**). In planning the route to the ABC-tricyclic framework from the three-component adduct, we adopted the other radical reaction as the B-ring cyclization process. The convergent approach to **1** was planned on the basis of the two radical reactions (Chart 3). Tricycyclic **15** was designed as the advance intermediate toward **1** before adjusting the C10-stereochemistry and installing the C4-hydroxy, orthoester, and vanillyl ester groups. In turn, retrosynthetic disconnection of the C7–8 bond of **15** provided the AC-ring **16** possessing the C8-xanthate. The C8-xanthate was to be utilized as a precursor of the C8-radical, which would undergo B-ring formation by 7-*endo* cyclization. The C4-substituted AC-ring **17** could be accessible by application of the key three-component re-

Fig. 2. Rationale for the Stereochemical Outcome of the Aldol Reactions

Table 3. Three-Component Radical Reactions of O,Te-Acetal **5b**, **6**, and **13**^{a)}

Entry	Radical acceptor	Electrophile	Product	Yield ^{b)}
1				89% ^{c)}
2 ^{d)}				86%
3				77%
4				99%
5 ^{e)}				74%
6 ^{f)}				41%
7 ^{g)}				76%
8				86%
9 ^{e)}				87%

a) Reaction conditions: **5b** (1 eq), **6** (3 eq), **13** (3 eq), Et₃B (3 eq), CH₂Cl₂ (0.1 M), 0 °C, 15 min. b) Product was obtained as a single isomer. c) **14a** was obtained as the major isomer (dr=9:1). d) Ten equivalents of **13b** was used. e) Conditions: **5b** (1 eq), **6a** (2 eq), **13e** (5 eq), Et₃B (3 eq), CH₂Cl₂ (0.1 M), rt, 60 min. f) Two equivalents of **6a** was used. g) Conditions: **5b** (1 eq), **6a** (2 eq), **13g** (5 eq), Et₃B (3 eq), CH₂Cl₂ (0.1 M), 0 °C, 15 min.

action: the reaction of α -alkoxy bridgehead radical derived from **18**, 5-membered A-ring **6e**, and branched allyltributyltin **10c** should assemble the requisite carbon structure for the ABC-tricyclic framework. In this reaction, the pre-installed C9-stereocenter as O,Se-acetal was to be transferred onto the C9-tetrasubstituted carbon of **1** in a stereospecific manner, while the C10-configuration would be transferred from that of the TBS-oxy group in A-ring **6e**. The C-ring **18**, the precursor of the key α -alkoxy bridgehead radical species, possessed the

Chart 3. Synthetic Plan of Resiniferatoxin (**1**)

complex cyclohexane structure decorated with the five contiguous stereocenters (C8, 9, 11, 13, 14), along with the bridgehead O,Se-acetal and the caged orthoester structures. Toward the synthesis of C-ring **18**, we selected lactol **19**^{72,73} as the starting material from which a series of stereoselective transformations and optimization of the order of functionalization would be implemented.

Chart 4 illustrates the stereoselective synthesis of C-ring **18**. The 8-step transformation converted chiral lactol **19** to 6-membered **20**, the C11–12 double bond of which was hydrogenated from the convex face of the cyclohexenone to set the C11-configuration. The C13-isopropenyl group was stereoselectively installed according to Knochel's protocol: treatment of **21** with a mixture of isopropenyl lithium and $\text{LaCl}_3 \cdot 2\text{LiCl}$ provided **22** as the single isomer.^{74,75} The TBS group of **22** was removed with tetra-*n*-butylammonium fluoride (TBAF) to liberate the C9-secondary alcohol, which was subjected to 2-iodoxybenzoic acid (IBX)-oxidation to generate ketone **23**. After the 3-step protecting group manipulation, including removal of the acetonide, triisopropylsilyl (TIPS)-protection of the C8-hydroxy group, and 1-methoxyethylidene formation from the diol, lithiated ethyl vinyl ether was added to the C9-ketone of the thus obtained **26** by again employing Knochel's protocol from the less hindered face, affording **27** as a single diastereomer. Next, the C9,13,14-orthoester was formed by acid-promoted transesterification of **27**. The 17-step sequence from lactol **19** completed the installation of the five contiguous stereocenters into the C-ring and the caged orthoester structure.

Our focus next turned to the synthesis of the O,Se-acetal structure embedded in the C-ring. The electron-rich vinyl ether of **28** was chemoselectively oxidized with *m*-chloroperoxybenzoic acid (*m*-CPBA) in aqueous CH_3CN to the hydroxyketone, which was subjected to *tert*-butyl hydroperoxide (TBHP)-promoted Baeyer–Villiger oxidation to form the

Chart 4. The Stereoselective Synthesis of C-Ring **18**

carboxylic acid moiety. After transformation of the carboxylic acid of **30** into the mixed sulfonic anhydride, **31** was condensed with 2-mercaptopyridine *N*-oxide sodium salt **32** to Barton ester **33**. Photo-irradiation in the presence of (PhSe)₂ transformed Barton ester **33** to O₂Se-acetal **34**, then the TIPS group of **34** was removed with TBAF to afford **35**. The overall efficiency of the 5-step sequence (40% from **28**) arising from a series of highly stereo- and chemoselective transformations enabled preparation of a sufficient amount of **35** for optimizing the crucial three-component reaction. After screening several substrates for the three-component reaction, we noted that the structure of the C8-substituent proximal to the reacting C9-center affected the efficiency of the key coupling. The substrate satisfying our demands was found to be acetate **18**, which was synthesized from **35** by C8-stereo-inversion *via* an oxidation/reduction sequence and subsequent acetylation.

With the designed C-ring **18** in hand, we began the assembly of the 5/7/6-tricyclic framework with the three-component reaction of the three fragments (**18**, **6e**, and **10c**, Chart 5). Under reflux in chlorobenzene in the presence of V-40 (0.5 eq), the bridgehead radical **38**, which was generated from **18**, stereoselectively reacted with the double bond of **6ea** (5 eq) from the opposite side of the C1-TBS-oxy group. The

resultant α -carbonyl radical then captured branched allyltributyltin **10c** (5 eq), giving rise to adduct **17a** with the correct C9 and C10-stereocenters of resiniferatoxin (**1**). Saponification of the acetate of **17a** concomitantly eliminated TBSOH to afford **39a** in 27% yield over 2 steps. Although the three-component reaction resulted in a low yield of the desired product, the efficiency of the coupling was improved by using the other C1-isomer of the A-ring **6eb** that served as the more effective acceptor of the bridgehead radical **38**. Specifically, subsection of three fragments, **18**, **6eb** and **10c**, to the above conditions gave rise to **17b** in higher yield. The thus obtained **17b** was saponified, giving rise to **39b** in 56% overall yield from **18**. Importantly, the present three-component reaction realized the attachment of the C4-substituted 5-membered A-ring to the highly oxygenated C-ring and the stereospecific construction of the C9-tetrasubstituted carbon, without touching any of the acid- and base-sensitive functional groups.

The 7-membered B-ring was constructed in 2 steps from **39b**. First, the C8 hydroxy group of **39b** was converted into xanthate **16**.^{76,77} The obtained xanthate **16** was treated with *n*-Bu₃SnH and V-40 in xylene at 180°C under microwave irradiation to trigger the generation of the C8-radical **40**. The subsequent addition of the radical to the C6–7 olefin in the 7-*endo* manner led to the formation of the tricyclic compound **41** as the single product. Of note, the other two double bonds (C1–2 and C15–16) in **40** did not participate in the radical reaction. Furthermore, the radical cyclization installed the correct C8-configuration of **1**. This outcome would arise from the selective approach of the C6–7 double bond to the C8 radical from the α -face outside of the cyclohexane to avoid steric interaction with H11/H12. Overall, 5-step transformation from C-ring **18** constructed the 5/7/6-tricarbo-cyclic structure with establishment of the correct C8 and C9-stereocenters of **1**. Finally, the *tert*-butyldiphenylsilyl (TB DPS) group was removed with HF-pyridine, giving rise to **15** as a potential intermediate of resiniferatoxin (**1**).

4. Conclusion

Radical-mediated three-component reactions and a convergent approach to the ABC-tricyclic framework of resiniferatoxin (**1**) were developed. An α -alkoxy bridgehead radical species was designed as the radical donor and was generated from O₂Se- or O₂Te-acetals by two different protocols. Stannyl radical was utilized to generate the α -alkoxy bridgehead radical from O₂Se-acetal **5a**, which underwent coupling with cyclic α,β -unsaturated ketones **6** and allyltributyltin **10b** *via* two radical reactions. Three-component reaction by the radical/polar crossover mechanism was pursued by using O₂Te-acetal **5b**, cyclic α,β -unsaturated ketones **6**, and aldehyde **13** employing the Et₃B/O₂ system. In both methods, the multiple reaction process and the stereoselectivity were effectively controlled, leading to the formation of functionalized 2,3-*trans*-disubstituted cyclopentenones **11** and **14**. One of the established methods was applied to the convergent assembly of the ABC-tricyclic framework of resiniferatoxin (**1**). The three-component reaction of the bridgehead radical of the highly functionalized C-ring, 5-membered A-ring **6eb**, and allyltributyltin **10c** produced the C4-branched AC-ring structure as the single product. The 7-membered B-ring was constructed by the radical reaction: the 7-*endo* cyclization of xanthate **16** constructed the tricyclic framework possessing

the correct C8 and C9-stereocenters of **1**. The present study demonstrated the power of the three-component reaction using an α -alkoxy bridgehead radical in constructing the fused carbocycles of the complex diterpenes. Further study towards the total synthesis of resiniferatoxin (**1**) from the synthesized **15** is underway in our laboratory.

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