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Radical-induced expeditious stereoselective synthesis of 2-alkyl 3-allyl *trans*-2,3-dihydrobenzofurans (TADHBs)

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ABSTRACT

A thorough study on radical-induced cyclopropyl ring fragmentation with encompassed olefinic and cyclopropane environment has been performed. Interestingly, the fragmentation has occasioned onto a stereoselective synthesis of 3-allyl *trans*-2,3-dihydrobenzofurans with impressive yields. The *trans*-dihydrobenzofurans are present as central core in many molecules of medicinal interest and the present protocol deliver a straight forward access to the embedded molecular architecture.

GRAPHICAL ABSTRACT

ARTICLE HISTORY
Received 31 August 2017

KEYWORDS
Allyl benzofuran; cyclopropyl ring cleavage; dicyclopropane; radical; stereoselective

Introduction

Radical-induced ring annulation has been always a subject of interest for shorter reaction times and delivering interesting outcomes.[1,2] Particularly, radical-induced ring annulations have been in focus in the course of natural product syntheses like triquinanes,[3–6] and lignans.[7,8] Thus, radical-induced tandem ring opening of reactive 3-membered rings like cyclopropanes and oxiranes, along with concomitant ring annulation with participating adjacent olefinic bonds, can be projected as a firm strategy for the synthesis of both carbocycles and oxacycles. Interestingly, only a few reports have appeared.[4,5,9–13] In this connection, the related dihydrobenzofurans (DHBs) have been a moiety of great interest to the chemistry community during the last two decades. The reason being, they function as a central core to important scaffolds of medicinal interest.[14–17] With our continued interest in benzoxacyclic natural products,[18–23] and the enhanced bioactivity[24] associated with these *trans* benzofurans as compared to their *cis*-counterparts, prompted us to deliver an important consideration in this direction. Interestingly, varied substituent patterns, particularly at the 2 and 3 positions in the DHBs have been associated with inspired

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structure reactivity relationships, proclaiming the honored status of this heterocycle.[24,25] Notably, neolignans (**B**) exhibit a broad biologically active profile,[8,26–29] the furaquinocins (**C**) reveal significant antibiotic activity,[30–32] (Fig. 1) whereas the single-dihydrobenzofuranol molecules (**D** and **D′**) disclose a huge range of bactericidal, antimicrobial, and pharmacological activities.[33] The fargenin **(E)** family of sesquineolignans, first reported by Moriyama et al.[34] bears a 3-allyl-2,3-dihydrobenzofuran as a central core. A course of recent strategic synthesis by Denton and Scragg[35] triggers intensive interest on these molecules due to their *in vitro* neurite outgrowing tendencies. A recent report from the Carreaux group describes a cross-metathesis isomerization allylation sequence to develop these bioactive neolignans bearing the dihydrobenzofuran core.[24] The protocol ends up with a planned preparation of 2-substituted-3-vinyl *trans*-dihydrobenzofuran that was successfully transformed into the desired natural products through multistep reaction sequences.

To date, elegant strategies like cycloadditions,[24] oxidative cross-couplings,[24] C–H insertions[24] are commonly used to achieve the stereoselective construction of these *trans*-dihydrobenzofurans. Further substitution to the 3-allyl *trans*-2,3-dihydrobenzofurans (TADHBs) would resemble an enviable molecular architecture, as a planned functionalization of the allyl moiety would facilitate emphasizing routes toward complex molecular frameworks. To the best of our knowledge, there have been no reports on stereoselective construction of TADHBs. We envisioned that radical-induced tandem cyclopropyl ring fragmentation of phenylcyclopropanes followed by a favorable 5-*exo*-*tet* ring annulation can be a painless access toward the targeted *trans* allyl DHBs. Trials were initiated to study the radical-mediated cyclopropyl ring fragmentation with properly premeditated phenylcyclopropanes. It was envisioned that a radical environment could possibly initiate radical-induced cyclopropane ring opening followed by a tandem ring closure to deliver such desired bicyclic core (Scheme 1, summarizes the initial retrosynthetic plan toward such ring cyclization). It was gratifying to discover that an appropriately planned combination of aryloxycyclopropane and phenylcyclopropane provided effective substrates for radical-induced synthesis of such TADHBs in overall 80% yields in all cases. Herein, we report the first successful radical-induced stereoselective synthesis of these TADHBs.

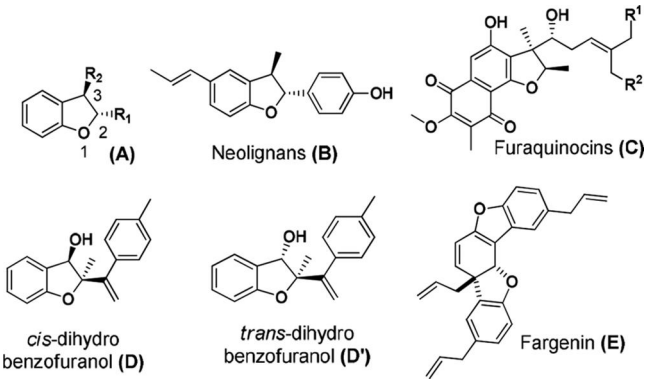
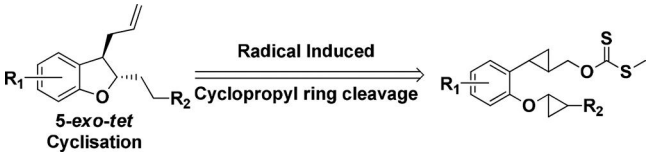


Figure 1. Natural products containing *trans*-2,3-dihydrobenzofuran.



Scheme 1. Retrosynthetic approach toward TADHBs.

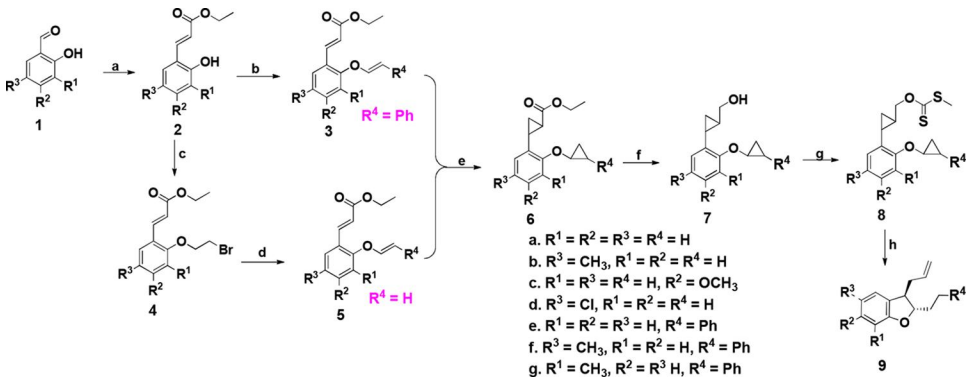
Results and discussion

To accomplish our plan, a suitably engineered dicyclopropane substrate was necessary. The appropriately substituted salicyldehyde **1** underwent a Wittig–Horner olefination to deliver the unsaturated ester **2**. The ester was then alkylated with 1,2-dibromoethane to form alkylated ester **4a–d** followed by a DBU-mediated dehydrohalogenation to generate the *O*-vinyl ether **5a–d**. The preplanned dicyclopropane ester **5a–d** was achieved by treating the *O*-vinyl ether **4a–d** with excess of diazomethane. The dicyclopropane ester **6a–d** was reduced to the corresponding alcohol followed by transformation to the corresponding xanthate **8a–d**. We were now ready with our intended attempt to develop the much awaited radical-mediated cyclopropyl ring cleavage. Interestingly, the dicyclopropyl ring fragmentation went as per our expectation delivering stereoselectively the 3-allyl *trans*-2,3-dihydrobenzofuran **9a–d** in excellent yields. To check the scope of the mapped methodology, the *O*-cyclopropane was replaced by *O*-cyclopropyl benzene **6e–g** (Scheme 2).

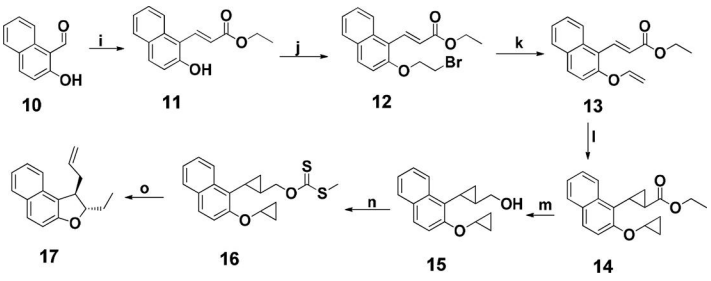
Similar results were obtained with 2-hydroxy-1-naphthaldehyde (**10**) as a starting precursor (Scheme 3).

The multiple NOE studies (Fig. 2) confirmed the *trans* relationship at 2- and 3-stereocentric positions.

All substrates illustrated in Table 1 delivered the 3-allyl *trans*-2,3-benzofuran in impressive yields in every case. Thus, this protocol presents an unbiased and rapid stereoselective way to prepare this specialized class of benzofurans. It was concluded that



Scheme 2. Reagents and conditions: (a) ethyl 2-(triphenylphosphoranylidene) acetate, toluene, 0 °C → RT, 3 h; (b) 2-bromovinyl-benzene, CuCl, $(Boc)_2O$ anhydride, toluene, reflux, 12 h; (c) 1,2-dibromoethane, K_2CO_3, acetone, reflux, 6 h; (d) DBU, THF, reflux, 6 h; (e) CH_2N_2, $Pd(OAc)_2$, Et_2O, 0 °C → RT, 1 h; (f) LAH, THF, 0 °C → RT, 5 h; (g) NaH, CS2, MeI, THF, 0 °C → RT, 18 h; and (h) TBTH, AIBN, toluene, reflux, 3.5 h.



Scheme 3. Reagents and conditions: (i) ethyl 2-(triphenylphosphoranylidene) acetate, toluene, 0 °C → RT, 3 h; (j) 1,2-dibromoethane, K_2CO_3, acetone, reflux, 6 h; (k) DBU, THF, reflux, 6 h; (l) CH_2N_2, $Pd(OAc)_2$, Et_2O, 0 °C → RT, 1 h; (m) LAH, THF, 0 °C → RT, 5 h; (n) NaH, CS2, MeI, THF, 0 °C → RT, 18 h; (o) TBTH, AIBN, toluene, reflux, 3.5 h.

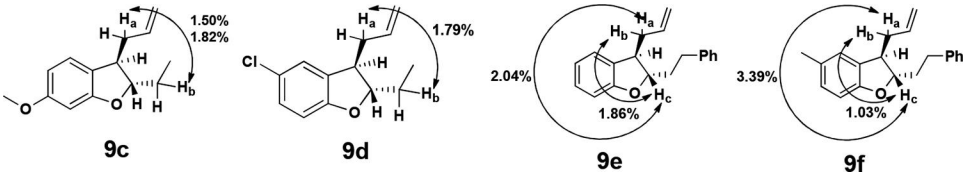


Figure 2. NOE study.

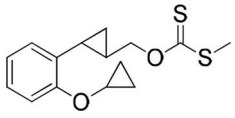
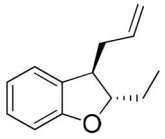
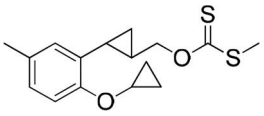
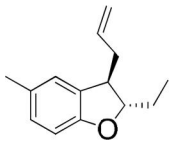
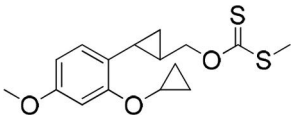
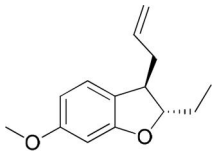
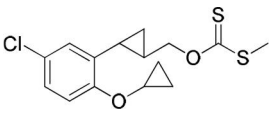
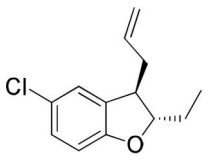
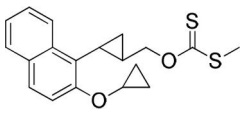
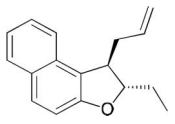
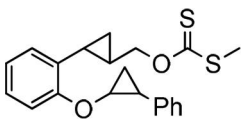
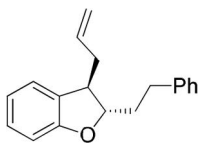
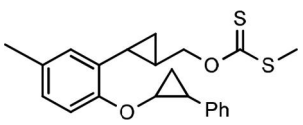
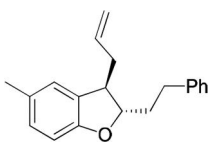
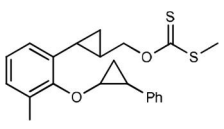
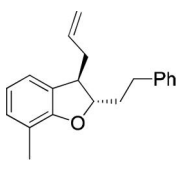
electron-withdrawing and electron-donating substituents displayed no effect on the 5-*exo-tet* ring annulation.

At this point, it appeared to us that a logical extension of this methodology could be applied to develop 1-allyl-2-alkyl-2,3-dihydro indenes **23** and 4-allyl-2-alkyl chromans **30**. But to our despair, when the similar reaction sequence was performed with suitably designed dicyclopropyl ester **19**, the product was the alkene **22** with the cyclopropyl ring remaining intact (Scheme 4).

Similar results were obtained from the homologated dicyclopropane ester **26** (Scheme 5).

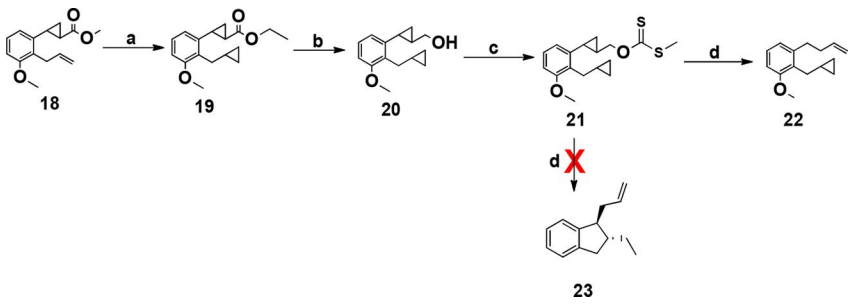
The reaction mechanism is proposed to follow an initial radical-induced cyclopropyl carbinyl homoallyl rearrangement followed by intramolecular S_H2 like process which opens up the second cyclopropane resulting in the 5-*exo-tet* ring closure. Such S_H2 reactions have been rarely reported in the literature.[36–39] The overall stability gained after the relieved 3-membered ring strain may be the key factor for such ring closure. Further, the stereoelectronic factors arising from the proximal cyclopropane and the annealed aromatic core may have accelerated the initial ring fragmentation. It is also proposed that the further driving force of the concomitant ring opening may be attributed to a stereoelectronic interaction (negative conjugation)[40,41] (Scheme 6) arising out of the alignment of one of the lone pairs of the oxygen atom with the adjacent cyclopropane which activates the tandem ring opening followed by the ring closure. This proposition receives further confirmation when no ring annulation occurs with substrates **19** and **26**, which clearly manifests the importance of the proximal oxygen atom adjacent to the cyclopropane in the starting precursors. The stereoselective formation of the *trans* junction can be attributed to a highly stabilized benzylic radical-reactive intermediate [**A**] and also the overall thermodynamic stability gained due

Table 1. Substrate view.

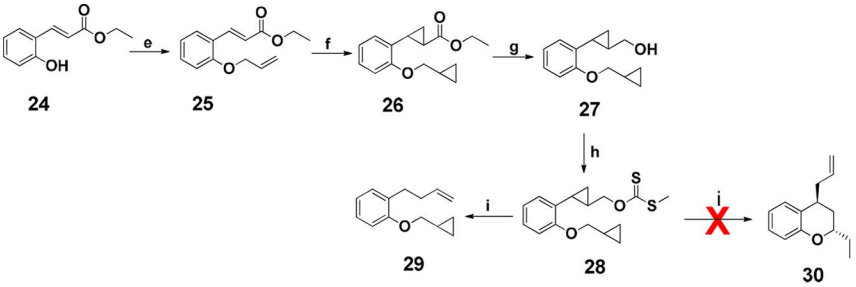
Entry no.	Xanthate	Product (relative *trans* stereochemistry)	Yield (%)
1			87
2			92
3			82
4			87
5			90
6			85
7			90
8			82

to the favorable *trans* stereochemistry. It is further proposed that the constructed *trans* stereochemistry of the DHB also acts as a hindrance toward further ring annulations.

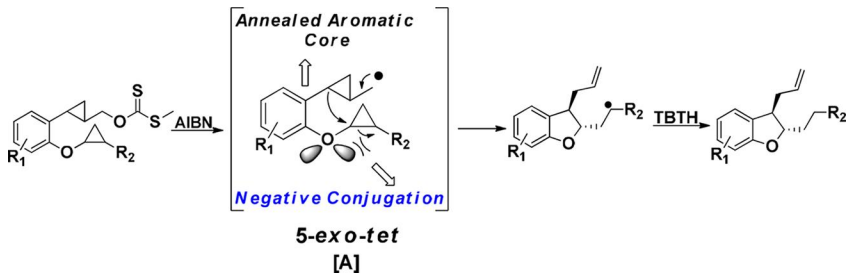
As an additional support, the DFT study also concludes that the *trans*-dihydrobenzofuran is more thermodynamically stable isomer than the corresponding *cis*-dihydrobenzofuran by 7.308kj/mol which additionally supports the stereoselective generation of the *trans* isomer (Fig. 3). The sets B3LYP/6-311 + G(d,p) and MP2/6-311 + G(d,p) were used for optimization and single point simultaneously were used in DFT study.



Scheme 4. Reagents and conditions: (a) CH_2N_2, $Pd(OAc)_2$, Et_2O, 0 °C, 1 h; (b) LAH, THF, 0 °C → RT, 5 h; (c) NaH, CS2, MeI, THF, 0 °C → RT, 18 h; (d) TBTH, AIBN, toluene, reflux, 3.5 h.



Scheme 5. Reagents and conditions: (e) Allyl bromide, K_2CO_3, acetone, reflux, 6 h; (f) CH_2N_2, $Pd(OAc)_2$, Et_2O, 0 °C, 1 h; (g) LAH, THF, 0 °C → RT, 5 h; (h) NaH, CS2, MeI, 0 °C → RT, 18 h; (i) TBTH, AIBN, toluene, reflux, 3.5 h.



Scheme 6. Proposed reaction mechanism.

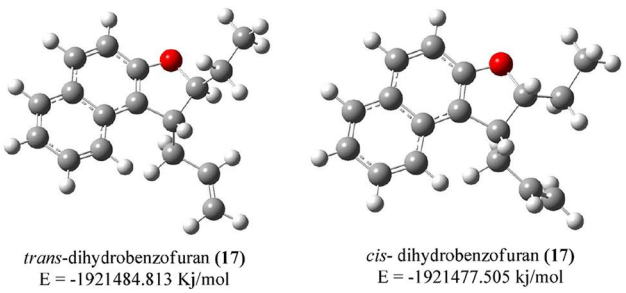


Figure 3. DFT calculation.

Conclusion

To conclude, a stereoselective synthesis of 2-alkyl-3-allyl-*trans*-dihydrobenzofuran has been developed using a radical-induced ring fragmentation of benzylic cyclopropanes. The reaction times are less and the overall yields are satisfactory in all cases. The aromatic substitutions do not exhibit any effect on the 5-*exo*-*tet* ring annulation. The common hindrances with free radical fragmentation like polymerizations are not visible at all. The manifested 3-allyl substituent can be an entry toward suitable directions with additional applications making this protocol as only methodology available till today for the construction of such TADHBs.

Experimental

General procedure for the synthesis of 9a–g, 17, 22, 29

To a well-stirred mixture of xanthate (4.2 mmol) in dry toluene (20 ml) in an oil bath at 110 °C under nitrogen atmosphere, azobisisobutyronitrile (1.22 mmol) was added. Tributyltin hydride (TBTH) (5.03 mmol) was added after 10 mins and allowed to stir at that temperature for 3.5 h. After the completion of reaction, solvent of reaction mixture was evaporated under reduced pressure. The crude mass was then purified by column chromatography using silica gel in specified solvent combination to deliver the desired compounds **9a–g, 17, 22, 29** with expected purity.

According to general procedure, xanthate **8a** (0.35 g, 1.19 mmol), TBTH (0.38 ml, 1.43 mmol) were used and elution with hexane. 0.19 g (1.04 mmol) of the target compound **9a** was obtained as a colorless liquid in 87% yield ($R_f = 0.8$; 5% EtOAc in hexane). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.76$–0.80 (m, 3H), 0.89–0.91 (m, 1H), 2.28–2.34 (m, 2H), 2.65–2.68 (m, 2H), 3.73–3.77 (m, 1H), 4.94-4.98 (m, 1H), 5.00 (dq, $J = 17.2$, 1.6 Hz, 1H), 5.84–5.91 (m, 1H), 6.89–6.93 (m, 1H), 7.12–7.14 (m, 1H), 7.17–7.23 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 6.24$, 29.60, 33.76, 50.41, 77.21, 112.20, 114.31, 120.40, 126.75, 129.63, 129.96, 138.57, 156.69 ppm. IR (Neat Film, NaCl): 2987, 1956, 1230 cm^{-1}. HRMS (ESI) calc'd for $C_{13}H_{16}O$ $[M]^+$: 188.1201, Found: 188.1200.

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