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Stereocontrolled synthesis of 2-alkenyl-4-methylene tetrahydropyrans

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Abstract—A variety of 2-alkenyl-4-methylene tetrahydropyrans were synthesized via consecutive transition metal-catalyzed bond forming processes. In this approach, ruthenium-catalyzed coupling of homoallylic carbonates and homopropargylic alcohols generates substrates containing the requisite functionality for a palladium-mediated cyclization, thereby providing concise access to the target structures. The installation of a trisubstituted alkene at the C-2 position was achieved using an olefin cross metathesis process.

Functionalized tetrahydropyrans are structural motifs found in many marine- and terrestrial-originated biologically active natural products such as phorboxazoles,[1] bryostatins,[2] and zampanolide.[3] The tetrahydropyran building blocks incorporated in these natural products are often decorated with both 2-alkenyl and 4-methylene functionality, thereby providing 2-alkenyl-4-methylene tetrahydropyran subunits represented by a general structure **1** (Scheme 1). There are a number of approaches developed for the construction of this functionality, which include the Prins-type cyclization[4] and a multi-step operation employing oxidation and olefination from **2**. A direct assembly of **1** from simple building blocks without the involvement of conventional multi-step transformations is rare and would constitute an effective synthetic tool. We envisioned that the implementation of transition metal-catalyzed carbon–carbon and carbon–heteroatom bond-forming processes would provide an effective entry to the preparation of this structural motif.

In the context of the total synthesis of natural products possessing the 2-alkenyl-4-*exo*-methylene tetrahydropyrans such as zampanolide, we planned to develop a general approach to construct this substructure via a streamlined use of three transition metal-catalyzed transformations; Ru-catalyzed ene–yne coupling, Pd-catalyzed C–O bond formation, and Grubbs catalyst-mediated cross-metathesis[5] (Scheme 2). The key step of our strategy is the Ru-catalyzed Alder-ene[6] type C–C bond formation, whereby direct installation of the *exo*-methylene unit and the precursor functionality for the π-allyl-Pd-mediated cyclization[7] will be achieved from alkene **4** and alkyne **5**. Subsequent ring closure reaction of **6** would provide tetrahydropyran **7**, which possesses an *exo*-methylene and the pendent vinyl group. One of the limitations of this strategy is the difficulty of installing a trisubstituted vinyl group. This is due to the low reactivity of the Ru-catalyzed Alder-ene type reaction for an alkene partner **4** possessing a branched carbon at the allylic center to give a trisubstituted olefin product **6**.[8] Another difficulty is to install a tertiary carbonate with defined configuration on the alkene substrate **4**. Faced with this encumbrance, we designed a new strategy in which the cross metathesis reaction between the terminal alkene of **7** (R_2 = R_2 = H) and appropriate olefins is used in order to expand the range of substrates available by this method, including the trisubstituted vinyl group. Recently, Trost and Machacek[9] have published an approach for the synthesis of five- and six-membered oxygen and nitrogen heterocycles utilizing Ru-catalyzed ene–yne coupling and Pd-catalyzed carbon–heteroatom bond formation in the context of developing a one-pot heterocyclization. We report herein an efficient and stereocontrolled synthesis of a variety of functionalized 2-vinyl-4-methylene tetrahydropyrans from homochiral, homoallylic carbonates **4** and homopropargylic alcohols **5**.

Keywords: 2-Alkenyl-4-methylene tetrahydropyrans; Ruthenium-catalyzed coupling; Palladium-catalyzed C–O bond formation.
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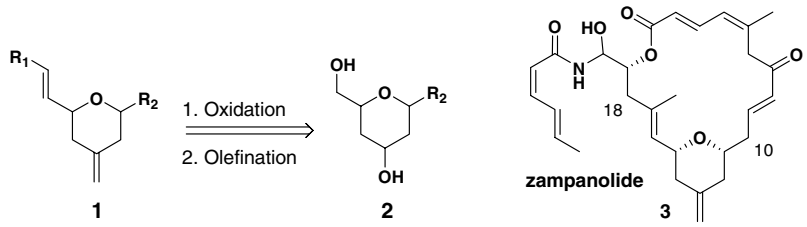
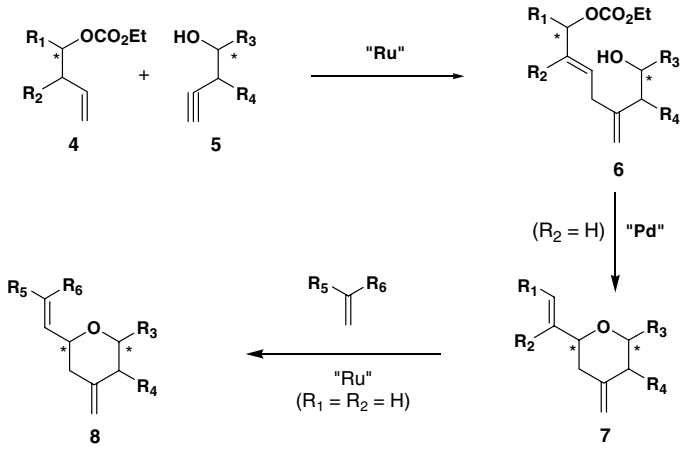


Scheme 1.



Scheme 2.

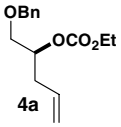
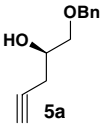
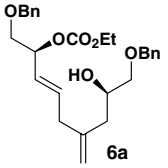
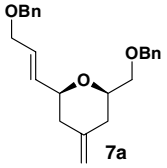
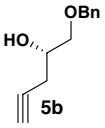
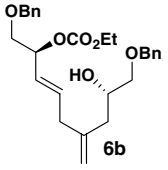
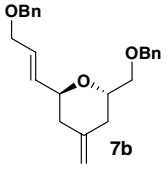
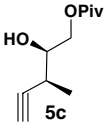
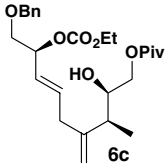
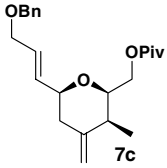
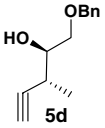
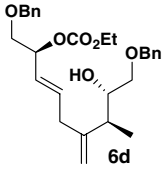
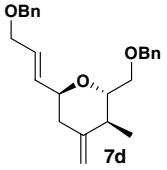
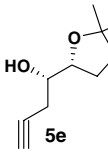
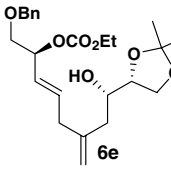
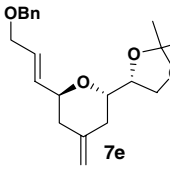
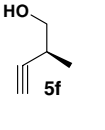
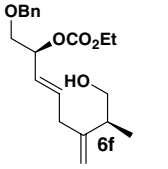
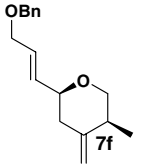
To test the validity of our plan, the ethyl carbonate derived from racemic 4-pentene-2-ol and racemic 4-pentyne-2-ol ($R_1 = R_4 = Me$, $R_2 = R_3 = H$) were treated with $CpRu(CH_3CN)_3PF_6$, (10 mol%) to give the desired branched isomer with complete selectivity in 65% yield. The Pd-catalyzed cyclization of this substrate produced a 1:1 mixture of racemic 2,6-*cis* and 2,6-*trans* diastereomers that are readily separated by chromatography. Encouraged by this result, a variety of structurally more elaborated tetrahydropyrans were synthesized employing readily available enatiomerically enriched homoallylic and homopropargylic alcohols (Table 1).

The ruthenium catalyzed coupling proceeded with modest yields (40–60%) and excellent selectivity for the branched isomer in most of the cases. Under the standard conditions[10] developed by Trost et al.[6c] the branched isomers **6a**–**f** were generated predominantly or exclusively from the combinations of alkene **4a** and alkynes **5a**–**f**. Subsequent palladium catalyzed cyclization[11] proceeded without difficulty thereby providing the tetrahydropyrans **7a**–**f** in 70–85% yield. The only minor side product in this reaction results from the β-hydride elimination of the π-allyl-Pd complex to form the conjugated tri-ene. The transfer of stereochemistry from the starting materials to the final tetrahydropyrans is exemplified in entries 1 and 2. Starting with suitable stereochemistry on alkenes and alkynes, the more thermodynamically favorable *cis*-2,6-disubstituted tetrahydropyran **7a** was obtained in 71% yield (entry 1) while the reversed stereochemistry of the homopropargylic alcohol gave the *trans*-2,6-disubstituted isomer **7b** with equal efficiency (entry 2). The structures of both isomers were confirmed by NOE experiment, showing a positive NOE enhancement between protons at the C2 and C6 positions for *cis*-isomer **7a** while no NOE between these protons for *trans*-isomer **7b**. This Pd-mediated-ring closure process is not sensitive toward the stereochemistry of the substituents in the 5-position (entries 3 and 4). Both substrates **6c** and **6d** possessing axial and equatorially disposed methyl groups were effectively cyclized to the corresponding tetrahydropyrans.

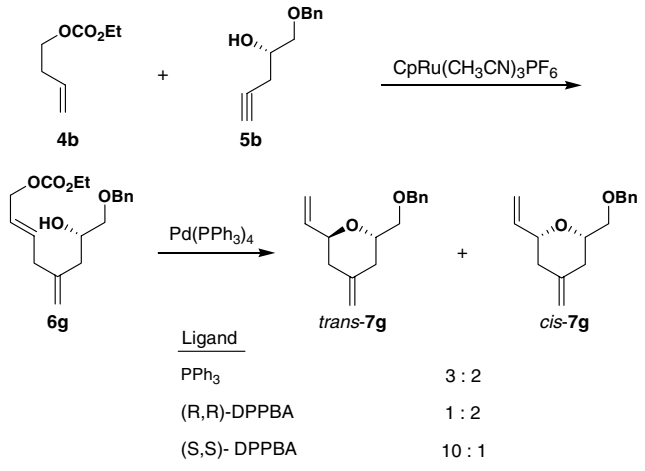
For the preparation of tetrahydropyrans with an unsubstituted vinyl group such as **7g**, alkene **4b** was coupled with **5b** to give the terminal allylic carbonate **6g** in 44% yield (92% BORSM) that lacks stereochemical information at the allylic carbon (Scheme 3). Cyclization of this substrate gave both *cis*- and *trans*-isomers in 3:2 ratio and overall 77% yield. The tendency for formation of the *cis*-isomer in the Pd-catalyzed ring closure could be enhanced to 10:1 by using Trost's (*R*,*R*)-DPPB ligand[12] while using the (*S*,*S*)-DPPB ligand reversed the ratio to 1:2 in favor of the *trans*-isomer.

The effectiveness of the Ru-mediated Alder-ene reaction was greatly diminished for generating a tri-substituted double bond. As seen in Scheme 4, the allylic carbonate **4c** gave only 20% of the desired product **6h**. When the epimeric carbonate **4d** was coupled to the same alkyne, only 10% of the product was isolated with a 1:1 ratio of branched to linear isomers. Unexpectedly, the Pd-mediated cyclization of substrate **6h** under the standard conditions was also problematic. A higher reaction temperature (70 °C) was required for the ionization of the carbonate compared to the room temperature reaction

Table 1. Tetrahydropyrans from the coupling of **4a** and **5**

Entry	Alkene	Alkyne (**5**)	Coupled product[a] (**6**)	Yield (BORSM[b])	Cyclized product[c] (**7**)	Yield
1	 **4a**	 **5a**	 **6a**	45 (63)	 **7a**	71
2	**4a**	 **5b**	 **6b**	61	 **7b**	68
3	**4a**	 **5c**	 **6c**	55	 **7c**	70
4	**4a**	 **5d**	 **6d**	51 (72)	 **7d**	85
5	**4a**	 **5e**	 **6e**	41	 **7e**	85
6	**4a**	 **5f**	 **6f**	47 (60)	 **7f**	70

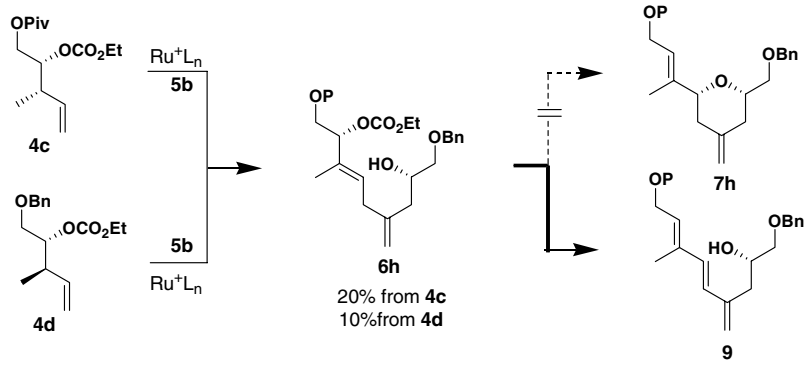
[a] Reaction performed at room temperature with 1.5 equiv alkene, 1.0 equiv alkyne at 0.5 M in DMF.
[b] BORSM yield is based on recovered alkyne.
[c] Reactions performed with 5% $Pd(PPh_3)_4$ in THF at 25 °C.



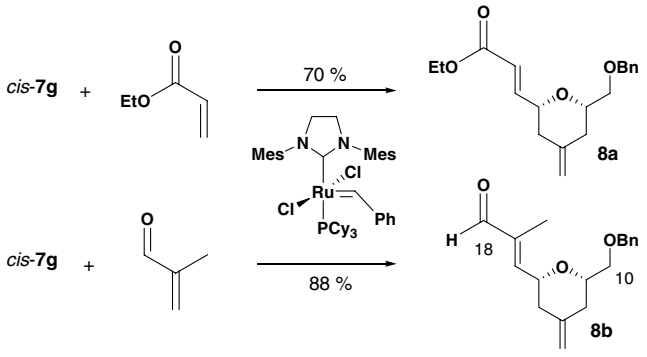
Scheme 3.

of other allylic carbonates **6a**–**g**. Yet under these conditions, only the eliminated product triene **9** was isolated without any indication of the formation of **7h**. The formation of triene **9** is believed to be the consequence of a faster reductive elimination than nucleophilic attack on the intermediate π-allyl-Pd complex by the hydroxyl group.

To expand the scope of the Ru-catalyzed Alder-ene type C–C bond formation and the π-allyl-Pd-mediated cyclization strategy toward the construction of a wider variety of alkene-substituted 4-*exo*-methylene tetrahydropyrans, a stereoselective cross metathesis[5b] between the mono-substituted vinyl group of **7g** and acrylate derivatives was envisaged. When *cis*-**7g** was treated with 10 mol% of Grubbs second generation catalyst in the presence of ethyl acrylate, the cross-coupled product **8a** was isolated in 70% yield with complete *E*-selectivity.



Scheme 4.



Scheme 5.

A similar reaction between *cis*-**7g** and methacrolein generated **8b** containing a trisubstituted *trans*- double bond in 88% yield. In each case, a small amount of pyran dimer was formed that was inert to the reaction conditions. Pyran **8b** represents the C10–C18 subunit of the natural product (+)-zampanolide, generated in only three steps from readily available starting materials (Scheme 5).

In summary, we have developed an efficient approach to synthesize various 2-alkenyl-4-*exo*-methylene tetrahydropyrans. In this strategy, various homoallylic carbonates and homopropargylic alcohols were coupled via the ruthenium-catalyzed Alder-ene type reaction and cyclized via palladium-mediated C–O bond formation to give the target structures. Introduction of a trisubstituted alkenyl group at the C-2 position was realized via cross metathesis catalyzed by Grubbs carbene complex.

Acknowledgements

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Supplementary data

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.07.063.

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Toste, B. M.; Sperrle, M. *J. Am. Chem. Soc.* **2001**, *123*, 12504–12509; (d) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695–705; (e) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067–2096.

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8. Examples of forming trisubstitued double bonds using the ruthenium-catalyzed Alder-ene reaction are rare.
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10. Ethyl carbonate **4a** (167 mg, 0.631 mmol) and alkyne **5b** (100 mg, 0.526 mmol) were combined in 1 mL DMF. $CpRu(CH_3CN)_3PF_6$ (23 mg, 0.0526 mmol) was added and the reaction was stirred for 2 h at room temperature. Water (2 mL) was then added and the product was extracted with ether. The extracts were combined, dried and concentrated in vacuo and the residue was chromatographed on silica gel (5:1, hexane/ethyl acetate) to give 146 mg (61%) of **6b** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 10H), 5.84 (dt, J = 15.5, 6.9 Hz, 1H), 5.51 (dd, J = 15.2, 7 Hz, 1H), 5.29 (td, J = 7, 4.7 Hz, 1H), 4.86 (br s, 2H), 4.56 (s, 2H), 4.55 (s, 2H), 4.18 (q, J = 7.1 Hz, 2H), 3.95 (m, 1H), 3.52 (m, 4H), 3.35 (dd, J = 10, 7.9 Hz, 1H), 2.79 (d, J = 7.1 Hz, 2H), 2.18 (d, J = 6.8 Hz, 2H), 1.29 (t, 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.43, 143.70, 137.85, 133.11, 128.31, 128.24, 128.08, 127.60, 127.53, 126.55, 113.52, 76.79, 74.01, 73.23, 73.07, 71.27, 68.23, 63.79, 39.97, 38.92, 14.11; HRMS (ESI) calcd for $C_{27}H_{34}O_6$ $[MNa]^+$: 477.2253, found 477.2244.
11. In a flame-dried 25 mL round bottomed flask was placed $Pd(PPh_3)_4$ (8 mg, 0.006 mmol) in 0.5 mL of THF. Substrate **6b** (58 mg, 0.127 mmol) in 2 mL of THF was added to the flask. After 2 h the solvent was removed and the residue was chromatographed (5:1, hexane/ethyl acetate) to give 33 mg (68%) of **7b** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 10H), 5.84 (m, 2H), 4.78 (br s, 2H), 4.59 (s, 2H), 4.52 (s, 2H), 4.04 (d, J = 3.9 Hz, 2H), 3.87 (dt, J = 11.4, 2.5 Hz, 1H), 3.57 (m, 3H), 2.27 (m, 2H), 2.09 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.80, 138.50, 133.43, 128.57, 127.95, 127.80, 109.52, 78.41, 77.60, 73.64, 73.33, 72.41, 70.44, 40.90, 37.43; HRMS (ESI) calcd for $C_{24}H_{28}O_3$ $[MNa]^+$: 387.1936, found 387.1945.
12. (a) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327–9343; (b) Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc.* **1999**, *121*, 4545–4554; (c) Jiang, L.; Burke, S. D. *Org. Lett.* **2002**, *4*, 3411–3414; (d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921–2943.