

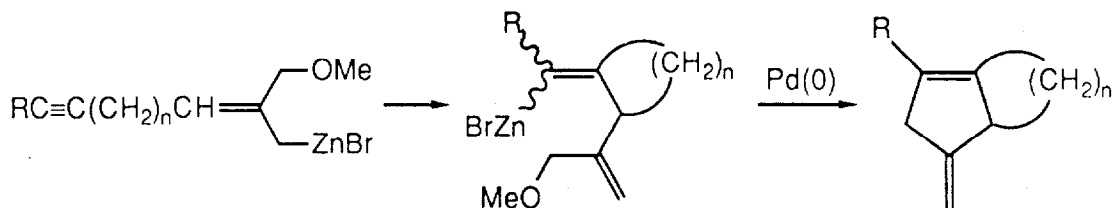
**1,5-ANNELATED 4-METHYLENECYCLOPENTENES BY
INTRAMOLECULAR TYPE I ZINC-ENE REACTIONS
FOLLOWED BY Pd(0)-CATALYZED CYCLIZATION**

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Summary: 3-(Alk-m-ynyl)-2-(methoxymethyl)-2-propenylzinc bromides **1** ($m = 4,5,6$) undergo intramolecular carbometallation. The products **2** were converted by Pd(0)-catalyzed cyclization to 1,5-annelated 4-methylenecyclopentenenes **3**.

Recently we reported a one-pot synthesis of 4-methylenecyclopentenenes by intermolecular addition of 2-(phenoxymethyl)- and 2-(benzyloxymethyl)allylzinc bromides to 1-trimethylsilylalkynes followed by *in situ* Pd(0)-catalyzed cyclization.¹ As a sequel to this study and in order to explore a convenient route to 1,5-annelated 4-methylenecyclopentenenes **3** we have subjected the 3-(alk-m-ynyl)-2-(methoxymethyl)-2-propenylzinc bromides **1** to the same protocol (Scheme 1).

The first step of the reaction sequence is a Type I intramolecular zinc-ene reaction,² which was found to take place with remarkable ease. In fact, it was possible not only to react **1a,b,c**, bearing an activating trimethylsilyl group,³ but also **1d**, in which the trimethylsilyl group is replaced by a deactivating alkyl group.⁴ Corresponding *intermolecular* allylzincations of similar internal alkynes do not occur.⁵ All starting materials **1** gave **2** regioselectively. NH₄Cl quench and NMR analysis of small



- 1 a** : R = TMS, n = 3
1 b : R = TMS, n = 4
1 c : R = TMS, n = 5
1 d : R = Buⁿ, n = 3

Scheme 1

samples of the zinc-ene reaction products indicated the presence of two geometric isomers of **2a,b,c** (H instead of ZnBr, ratio circa 9 : 1) and only one in case of **2d**. As expected, reaction temperature and reaction time were dependent on ring size (Table 1). Unknown by-products were formed together with the seven-membered ring compound **2c**.

The cyclization of **2** to **3** by a catalytic amount of Pd(PPh₃)₄ was accomplished quantitatively, without side reactions and under mild conditions (Table 1). Due to the configurational lability of (1-silyl-1-alkenyl)zinc compounds,⁶ both isomers of **2a,b,c** could be converted to **3**. Complete ring closure of **2d** clearly demonstrated the formation of the *syn* carbometallation product by the zinc-ene reaction.⁴

For the preparation of organozinc compounds **1** two different routes were followed (Scheme 2). Phosphonium salts **7a,b,c,d** were prepared according to standard procedures. **7a,b,d** were subjected to a Wittig reaction with α,α' -bis(tetrahydropyranyloxy)acetone **8**.⁷ After hydrolysis of **9a,b,d**, the diols **10a,b,d** were transformed into the mono methyl ethers **11a,b,d**. This conversion could only be accomplished in low yield. Therefore, **11c** was prepared by Wittig reaction of phosphonium salt **7c** with ketone **12**⁸ followed by hydrolysis of **13**. Chlorination,⁹ Grignard reagent formation,¹ and finally conversion to the organozinc compounds **1** (*cis/trans* mixtures) were carried out in identical ways on **11a-d**, **14a-d** and **15a-d**, respectively. The dynamic structure of allylmagnesium- and allylzinc compounds allowed both geometric isomers of the chlorides **14** to be transformed, *via* **15** and **1**, into the cyclization products **3**.

Table 1. Reaction conditions and yields of the reaction sequence **1** → **2** → **3**.

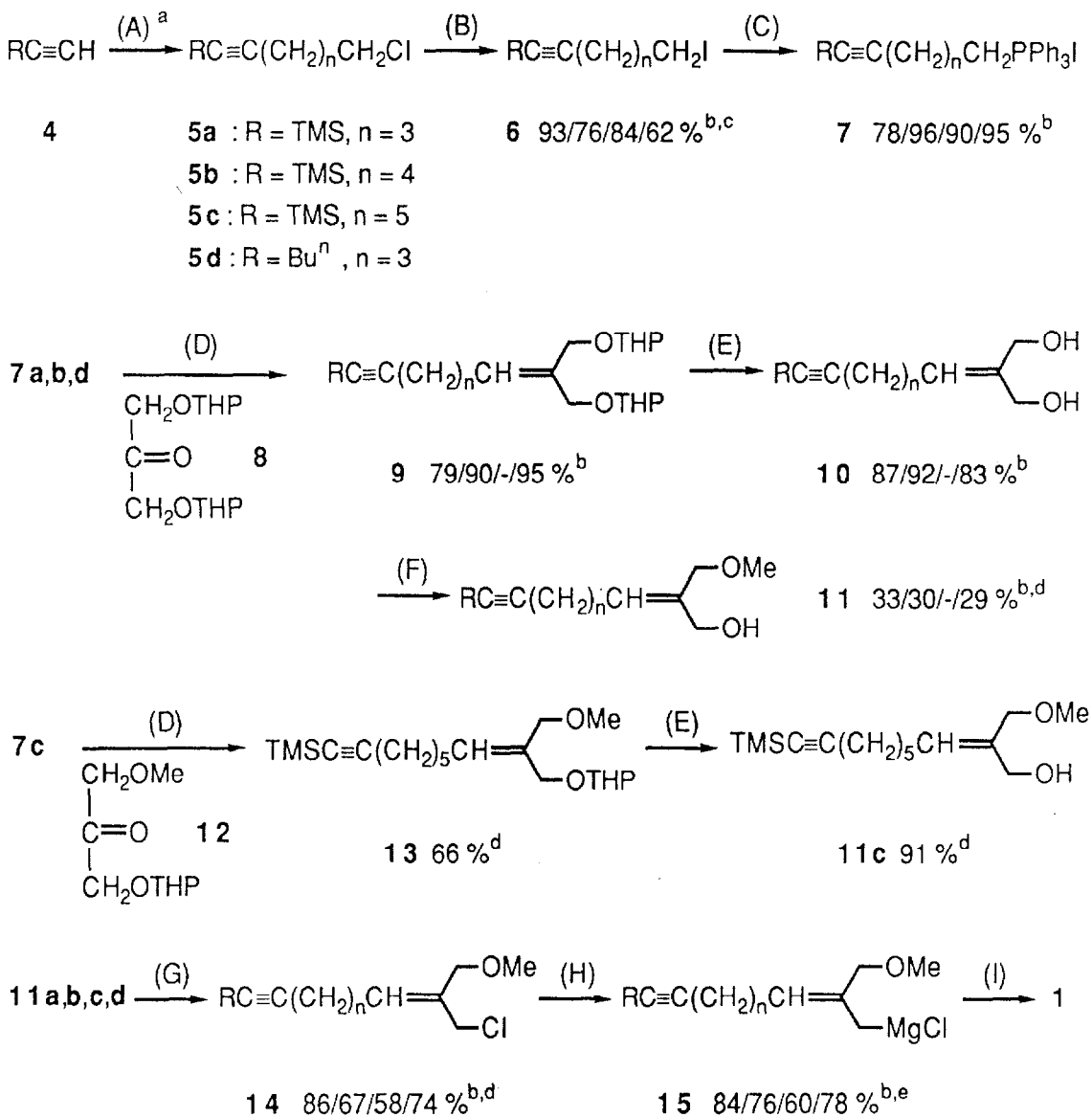
		Reaction conditions		Yield ^c of 3 ^{d/e} (%)	
Ene reaction ^a		Pd(0)-catalyzed cyclization ^b			
1 a	RT, 2h	RT,	3,5 h	-	/84
1 b	65°C, 2h	65°C,	2h ^f	67/52	
1 c	65°C, 24h	65°C,	4h ^f	44/-	
1 d	65°C, 8h	RT,	4h	75/73	

^a 7-20 mmol **1**. ^b Carried out *in situ*¹ by adding 5 mol% Pd(PPh₃)₄; work-up: aqueous NH₄Cl, ether, brine, MgSO₄, careful evaporation of solvent, evaporative distillation or GLC analysis.

^c Yields are based on the Grignard reagent **15** (Scheme 2). ^d Isolated yields. ^e GLC yields.

^f No cyclization at RT.

Scheme 2



^a Conditions. (A) 1. n-BuLi, n-hexane, THF, -20 °C, 0.5 h; 2. I(CH₂)_nCH₂Cl, RT, 90h; (B) NaI, acetone, reflux, 30h; (C) PPh₃, benzene (0.6 ml/mmol), reflux, 6h; (D) 1. n-BuLi, n-hexane, THF, -20 °C → RT, 4h; 2. **8** or **12**, -30 °C → RT, 64h; (E) Dowex 50W, X8, 200-400 mesh, MeOH, RT, 2h; (F) **10a,b**: 1. MeI (4 equiv.), THF; 2. NaH (1 equiv.), THF, 0 °C; 3. RT, 2h; **10d**: 1. NaH (1 equiv.), THF, reflux, 1h; 2. MeI (1 equiv.), RT, 18h; (G) 1. MesCl, LiCl, s-collidine, DMF; 2. ice-water, ether/pentane 1:1, saturated citric acid solution, NaHCO₃, brine; (H) See ref. 1, modifications: 4 mL THF/mmol **14**, duration of addition of **14**: 10h; (I) ZnBr₂ (1.5 equiv.). ^b Yields of **a/b/c/d**. ^c Yields of conversion **4** → **6**. ^d 1:1 mixture of *cis* and *trans* forms. ^e Grignard reagent formation was accompanied by formation of protonation and/or Wurtz coupling product(s).

In spite of many investigations in the field of *intermolecular* carbometallation of alkynes,¹⁰ reports concerning the *intramolecular* version are few.¹¹ In the present study, intramolecular Type I zinc-ene reactions of alkynes, leading to five-, six- and seven-membered rings, are described. Utilization of 3-(alk-m-ynyl)-2-(methoxymethyl)-2-propenylzinc bromides permits a second cyclization step, catalyzed by Pd(0), yielding ultimately 1,5-annulated 4-methylenecyclopentenes. Overall, bicyclic molecules apt for further elaboration are obtained from open-chain starting materials in a one-pot procedure.

References and Notes

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- 8 Ketone **12** was prepared by isomerization¹² of 3-O-methylglyceraldehyde¹³ to 1-hydroxy-3-methoxyacetone (4 mol% Et₃N, dioxane, reflux, 4h) followed by conversion to the THP ether (DHP, 10 mol% PPTS, CH₂Cl₂, RT, 60h; yield: 24%, based on 3-O-methylglyceraldehyde).
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