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SYNTHESIS OF VINYLCYCLOPROPANES VIA PALLADIUM-CATALYZED COUPLING OF CYCLOPROPYLZINC HALIDES WITH VINYL IODIDES. TOTAL SYNTHESES OF (±)-PREZIZANOL AND (±)-PREZIZAENE

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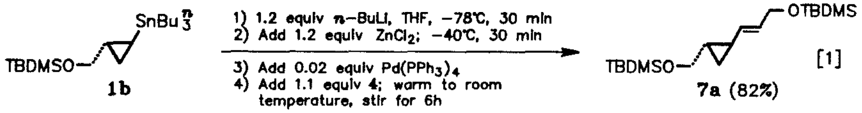
ABSTRACT: Palladium(0)-catalyzed coupling of cyclopropylzinc halides, readily prepared from the corresponding cyclopropyl(tri-n-butyl)stannanes, with vinyl iodides provides good yields of functionalized vinylcyclopropanes. The coupling reaction is used as a key step in total syntheses of the sesquiterpenoids (±)-prezizanol and (±)-prezizaene.

During the past 10 - 15 years, the coupling of organometallic reagents with structurally diverse organic halides has become a versatile and increasingly important method of forming carbon-carbon bonds.[1] For example, a wide variety of functionalized organic compounds are readily available by palladium- and nickel-catalyzed coupling of various organometallic species with aryl, alkenyl, and alkynyl halides.[1] Furthermore, also in the recent past, investigations into the use of functionalized cyclopropanes in organic synthesis have proven to be very fruitful.[2] In this regard, the synthetic uses of thermal rearrangements of vinyl- and 1,2-divinylcyclopropane systems have been particularly noteworthy. In this Letter, we describe a new method of preparing functionalized vinylcyclopropanes by palladium(0)-catalyzed coupling of cyclopropylzinc halides with vinyl iodides and illustrate the use of this reaction as a key step in total syntheses of the sesquiterpenoids (±)-prezizanol and (±)-prezizaene.

The reaction conditions employed for the overall coupling of the tri-n-butylstannylcyclopropane 1b[3,4] with the vinyl iodide 4[7] are given in Eq. [1].[9] In similar fashion, various combinations of tri-n-butylstannylcyclopropanes and vinyl iodides (1c[4] + 4,[7] 1b[4] + 5,[7] 1c[4] + 5,[7] 2c[4] + 5,[7] 2b[4] + 6a,[7] 3[4] + 5[7]) afforded the substituted cyclopropanes 7b, 8a,b, and 9 - 11, respectively, in the yields indicated in Chart 1. In each case, the reaction was quite clean and the product was purified by chromatography (silica gel) and distillation. In the preparation of compound 11, $ZnBr_2$ was used in the place of $ZnCl_2$ and, since the product 11 was difficult to separate from the vinyl iodide 5, a slight deficiency (0.95 equiv) of the latter material was employed. It can be seen that the reaction tolerates a number of different functional groups, the vinyl iodide coupling partner may possess an alkyl substituent on the carbon bearing the iodine (2b + 6a → 10), and the method is amenable to preparing 1,2-divinyl-(e.g. 11) as well as monovinylcyclopropanes.



[1]

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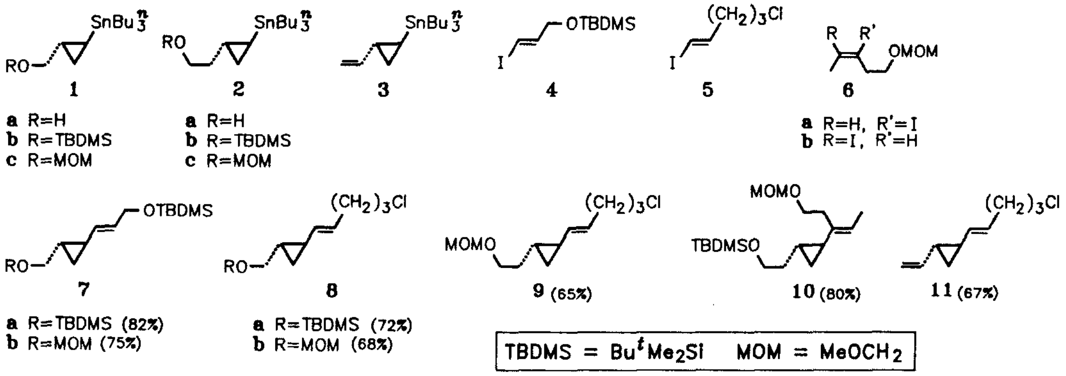


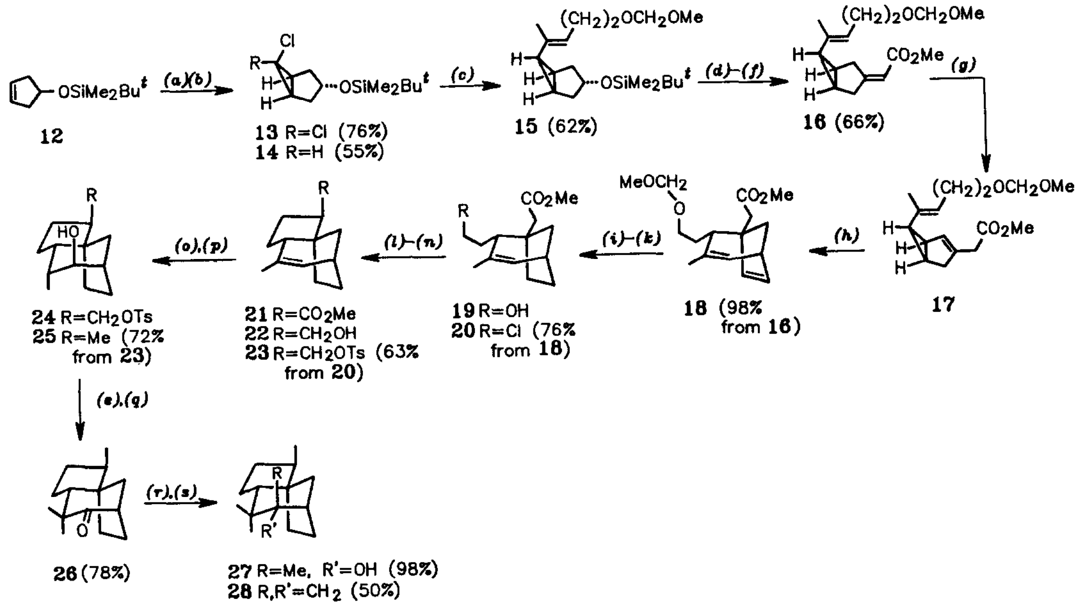
CHART 1

The sesquiterpenoid prezizaene (enantiomer of 28) was first isolated from vetiver oil of Reunion origin,[10] while (-)-prezizaene (28) and the related alcohol (-)-prezizanol (27) were obtained from *Eremophila georgei*.[11] Total syntheses of (-)-27 and (-)-28 have been reported.[12] Outlined in Scheme 1 are our total syntheses of (±)-27 and (±)-28 via a route in which the Pd(0)-catalyzed coupling of a cyclopropylzinc chloride with the vinyl iodide **6b**[7] played a key role.

Reaction of the silyl ether **12**[13] with dichlorocarbene gave primarily **13**, accompanied by a small amount of the corresponding *cis* isomer. Slow addition of a THF solution of **13** to a cold solution of *t*-BuLi in 3:1:1 THF-Et_2O-pentane, followed by protonation of the intermediate and subsequent chromatographic separation of the mixture of chlorocyclopropanes, provided the desired *endo* isomer **14** in 55% yield. Treatment of **14** with lithium 4,4′-di-*tert*-butylbiphenylide,[14] conversion of the resultant cyclopropyl-lithium reagent into the corresponding organozinc chloride, and $Pd(PPh_3)_4$-catalyzed coupling of the latter species with the iodide **6b** afforded **15**, which was converted efficiently via a 3-step sequence into the α,β-unsaturated ester **16**. Deconjugation of **16** gave **17**, which, upon distillation at 110 °C, underwent clean Cope rearrangement[15] to give the bicyclic diene **18**.

Chemoselective hydrogenation of **18**, followed by treatment of the resultant alkene with p-$MeC_6H_4SO_3H$-MeOH gave an inseparable equilibrium (3:2) mixture of the alcohol ester **19** and the corresponding lactone. Reaction of this mixture with Ph_3P-CCl_4-Et_3N, followed by chromatography of the product mixture, produced the desired chloride **20** (48%) along with the lactone (41%). The latter material could be recycled (p-$MeC_6H_4SO_3H$, MeOH; Ph_3P-CCl_4-Et_3N; separation) and, in this manner, a 76% overall yield of the chloride **20** from **18** was obtained after two recycles.

Examination of molecular models leads one to predict that intramolecular alkylation of the ester chloride **20** would provide mainly or exclusively the tricyclic ester **21**. In the event, treatment of **20** with *i*-Pr_2NLi in THF afforded **21**, accompanied by a small amount



Scheme 1. (a) $CHCl_3$, CH_2Cl_2, NaOH, H_2O, $PhCH_2Et_3NCl$; (b) t-BuLi, THF-Et_2O-pentane (3:1:1), -107 °C; HOAc, Et_2O, -107 °C; (c) (4,4′-di-tert-butylbiphenyl)$^{\dot{-}}$$Li^+$, THF, -78 °C; $ZnCl_2$, THF, 0 °C; **6b**, $Pd(PPh_3)_4$, THF, reflux; (d) n-Bu_4NF, THF; (e) $C_5H_5NCrO_3HCl$, NaOAc, CH_2Cl_2; (f) $[(MeO)_2POCHCO_2Me]Li$, THF; (g) i-Pr_2NLi, THF, -78 °C; HOAc, Et_2O, -78 °C; (h) 110 °C, 0.1 torr; (i) H_2, $(Ph_3P)_3RhBr$, C_6H_6; (j) p-$MeC_6H_4SO_3H$, MeOH, reflux; (k) CCl_4, Ph_3P, Et_3N, reflux; (l) i-Pr_2NLi, THF, -78 °C; (m) $LiAlH_4$, Et_2O; (n) p-$MeC_6H_4SO_2Cl$, 4-dimethylaminopyridine, CH_2Cl_2; (o) $BH_3{\cdot}Me_2S$, THF; H_2O_2, NaOH; (p) $LiEt_3BH$, THF; (q) KH, THF; MeI, THF, reflux; (r) MeLi, THF, -78 °C; (s) $MeSO_2Cl$, i-Pr_2NEt, CH_2Cl_2.

(~10%) of the epimeric ester.[16] Reduction afforded the corresponding alcohols (**22** + epimer), which were readily separated by chromatography of the corresponding tert-butyldimethylsilyl ethers.

A standard sequence of reactions was employed to convert the alcohol **22** into the racemic ketone **26**, which was spectrally identical with (-)-**26** previously synthesized by Vettel and Coates.[12,17] Treatment of **26** with MeLi provided (±)-prezizanol (**27**), which, upon dehydration, gave (±)-prezizaene (**28**). The latter materials gave IR and ^1H NMR spectra identical with those of (-)-**27**[17] and (-)-**28**,[17] respectively.

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REFERENCES AND NOTES

1. Kumada, M. Pure Appl. Chem., 1980, 52, 669; Negishi, E. Pure Appl. Chem., 1981, 53, 2333; Acc. Chem. Res., 1982, 15, 340; Heck, R. F. "Palladium Reagents in Organic

Syntheses," Academic Press Inc. (London) Ltd., London, England. 1985; Stille, J. K. *Angew. Chem. Int. Ed. Engl.*, **1986**, 25, 508, and references cited therein.

2. de Meijere, A. *Bull. Soc. Chim. Belg.*, **1984**, *93*, 241; Hudlicky, T.; Kutchan, T. M.; Naqvi, S. M. *Org. React.*, **1985**, *33*, 247; Paquette, L. A. *Chem. Rev.*, **1986**, *86*, 733; Piers, E.; Burmeister, M. S.; Reissig, H. U. *Can. J. Chem.*, **1986**, *64*, 180, and references cited therein; Piers, E.; Jung, G. L.; Ruediger, E. H. *Can. J. Chem.*, **1987**, *65*, 670.
3. All isolable substances reported herein exhibited spectra in accord with structural assignments and gave satisfactory high resolution mass spectrometric molecular mass measurements.
4. Compounds **1b,c** and **2b,c** were prepared by reaction of **1a** and **2a** with *t*-BuMe$_2$SiCl (imidazole, Me$_2$NCHO) or MeOCH$_2$Cl (*i*-Pr$_2$NEt, CH$_2$Cl$_2$). The alcohols **1a** and **2a** were acquired by cyclopropanation (CH$_2$I$_2$, Et$_2$Zn, PhMe, 40 °C)[5] of the corresponding alkenes, which were prepared by hydrostannylation (1.3 equiv *n*-Bu$_3$SnH, AIBN, 80 °C)[6] of 2-propyn-1-ol and 3-propyn-1-ol. Compound **3** was obtained from **1a** by oxidation (pyridinium chlorochromate, NaOAc, CH$_2$Cl$_2$), followed by Wittig olefination (Ph$_3$P=CH$_2$, THF).
5. Furukawa, J.; Kawabata, N.; Nishimura, J. *Tetrahedron*, **1968**, *24*, 53; Miyano, S.; Hashimoto, H. *Chem. Commun.*, **1971**, 1418.
6. *Cf*. Jung, M. E.; Light, L. A. *Tetrahedron Lett.*, **1982**, *23*, 3851.
7. The vinyl iodides **4** - **6** were prepared by hydrozirconation-iodination[8] of the corresponding alkynes. In the case of MeC≡C(CH$_2$)$_2$OCH$_2$OMe, this reaction produced a 1:1 mixture of **6a** and **6b**, which were separated by chromatography on silica gel. The isolated yields were: **6a**, 38%; **6b**, 36%.
8. Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.*, **1975**, *97*, 679.
9. For previous examples of transmetallation of tri-*n*-butylstannylcyclopropanes with *n*-BuLi, see Corey, E. J.; De, B. *J. Am. Chem. Soc.* **1984**, *106*, 2735; Corey, E. J.; Eckrich, T. M. *Tetrahedron Lett.* **1984**, *25*, 2415.
10. Andersen, N. H.; Falcone, M. S. *Chem. Ind. (London)*, **1971**, 62.
11. Carrol, P. J.; Ghisalberti, E. L.; Ralph, D. E. *Phytochemistry*, **1976**, *15*, 777.
12. Vettel, P. R.; Coates, R. M. *J. Org. Chem.*, **1980**, *45*, 5430.
13. For the parent alcohol, see Crandall, J. K.; Baker, D. B.; Colyer, R. A.; Watkins, R. J.; Arrington, J. P. *J. Org. Chem.*, **1968**, *33*, 423.
14. Freeman, P. K.; Hutchinson, L. L. *J. Org. Chem.*, **1980**, *45* 1924; **1983**, *48*, 4705.
15. Compound **17** rearranged slowly to **18** at room temperature. Interestingly, thermolysis of the *exo* isomer of **17** at various temperatures (155 - 220 °C, benzene, sealed tube) produced a plethora of products from which **18** could be isolated in only poor yield (~25%).
16. A separate experiment showed that this epimeric ester was formed by epimerization of the primary product **21**. Thus, treatment of **20** with a deficiency of *i*-Pr$_2$NLi gave exclusively **21**, accompanied by some starting material **20**.
17. We are very grateful to Professor Coates for copies of the IR and ^{1}H NMR spectra of (-)-**26**, (-)-prezizanol, and (-)-prezizaene.

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