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# A Simple and Practical Synthesis of 3,10-Disubstituted β-Pinene Derivatives

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***Key Words*** : $\eta^3$-Allyltitanium complexes; β-Pinene derivatives; Regiocontrol; Electrophiles.

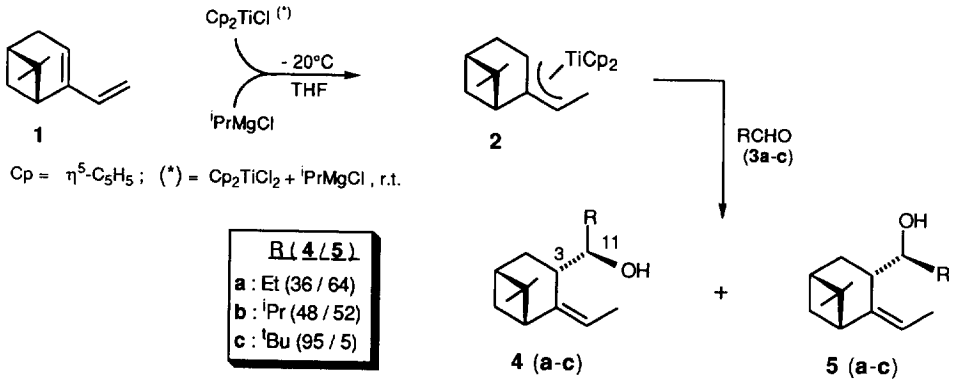
***Abstract*** *: The nopadiene - derived $\eta^3$-allyltitanium complex reacts with aldehydes regiospecifically at the ring carbon atom. Two diastereomeric (Z) 10-methyl-β-pinene-3-yl carbinols are isolated in a ratio depending on the aldehyde alkyl group. Other electrophiles can also be used instead of aldehydes. In this way, the ketone, ester, amide functions or hydrogen atom are introduced into the 3-position. Since other α-pinene derived dienes can also be employed, the procedure should be regarded as generally useful for the preparation of 3,10-bifunctionalized β-pinene derivatives.*

Allyl organometallic reagents are known to react with aldehydes to provide homoallylic alcohols.[1] High regio- and stereocontrol for such reactions are achieved with $\eta^3$–allyltitanocene complexes.[2] The latter can be readily prepared by reaction of titanocene dichloride with a Grignard reagent and diene,[3] and the possibility that functionalized allyltitanium reagents are directly available in this way has recently attracted our attention. Thus, the reagents derived from some substituted or incorporated dienes have been shown to react with electrophiles, providing a short route to versatile synthons.[4]

Pinene derivatives are widely occurring flavor and arome constitutents, that possess interesting biological properties.[5] Furthermore, if appropriately functionalized, they can be used as chiral starting materials[6] or ligands for asymmetric synthesis.[7] Thus, it appears worthwhile to develop selective methods of functionalizing the pinene skeleton. We report here that new 3,10-disubstituted β-pinene compounds can be obtained regio- and stereoselectively by means of the allyltitanation procedure, from the simple α-pinene - derived dienes .

## Results and Discussion

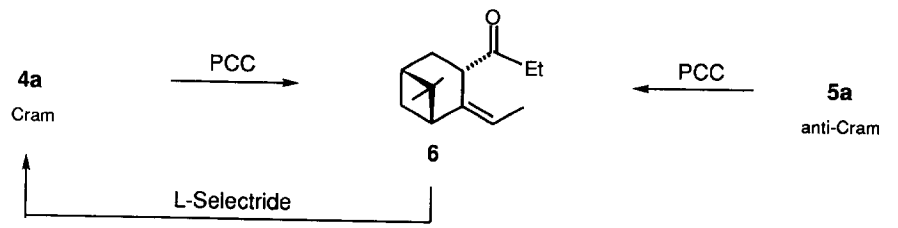
Nopadiene (**1**), which can easily be prepared from commercially available (-)-nopol,[8] was used as a starting diene. The allyltitanium complex **2** was formed in a one-pot reaction including two succesive reduction steps (Scheme 1): $Cp_2TiCl$ formed at first at room temperature was allowed to react with the second equivalent of isopropylmagnesium chloride in the presence of **1** at -20°C. As has been already explained,[3] only one of the two possible regioisomeric complexes, namely **2** was obtained. Complex **2** thus formed *in situ* was used directly in the addition reactions.




Scheme 1

When propanal (**3a**) was added to the THF solution of **2** at -20°C the color of the solution changed rapidly from brown to dark-red. After an additional stirring, the basic workup ($NaHCO_3$), followed by easy flash chromatography separation over $SiO_2$, gave two products. The latter have been shown to be diastereomeric homoallylic alcohols **4a** (18.7% yield) and **5a** (33.2% yield). Thus, the addition of aldehyde **3a** appears to occur regiospecifically at the ring carbon atom rather than at the side-chain atom. The formation of only two diastereomers is in accordance with an *endo* attack generally observed for pinene derivatives because of steric reasons.[9]

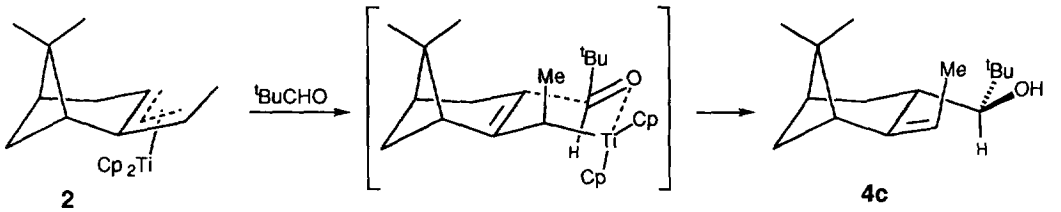
The configuration of carbon-3 in the two alcohols was ascertained by converting them as shown in Scheme 2. Alcohols **4a** and **5a** were oxidized with pyridinium chlorochromate in $CH_2Cl_2$ to afford the unique ketone **6** in both cases.[10] The latter was reduced with L-Selectride which is known to give Cram alcohol preferentially.[11] In this way, the minor isomer **4a** has been shown to possess Cram (3S, 11R) configuration. This assignment is in accordance with the $^1H$ NMR data. Thus, the $^1H$ NMR resonances corresponding to the carbinol H-C(OH) as well as to the gem-dimethyl protons differ significantly in **4a** and **5a**. The more deshielded δ values for **5a** (anti-Cram; 3S, 11S) than for **4a** are in accordance with the literature data reported for similar compounds.[12] Furthemore, nuclear Overhauser effect (NOE) measurements indicate that both stereoisomers have the unique (Z)-alkene geometry.




Scheme 2

We next examine the effect of modifying the aldehyde alkyl chain. The reactions employing isobutyraldehyde (**3b**) and pivalaldehyde (**3c**) were performed in the same manner and conditions as above. We noticed that increasing the steric hindrance at the α-carbon atom affects the stereochemical outcome of

the reaction. The diastereomer ratio **5/4** decreases markedly with size of the α-substitutent R (Scheme 1). Thus, unlike for **5a** predominant over **4a** (R=Et, see above) an almost equal mixture of both diastereomers **4b** and **5b** (R=$^{i}$Pr) was obtained, respectively in 29.7% and 32.2% yield. On the other hand, the isomer **5c** (R=$^{t}$Bu) appeared to be clearly minor over the isomer **4c** (46.5% yield). As should be emphasized, the reaction with t-BuCHO proceeded with striking regio- and stereoselectivity affording a practically unique carbinol of the six possible isomers.

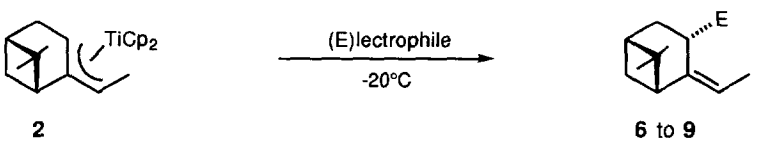



TS (pseudo-equatorial $^{t}$Bu)

Figure 1

The regiochemistry of the reaction is consistent with a reactant-like cyclic transition state,[13] involving an endocyclic position of the C=C bond (Figure 1). The stereochemical trend that we observed for the addition of aldehydes **3a-c** can be rationalized by assuming a conventional chair-like six-membered transition state (Figure 1). In such a case, the almost exclusive formation of **4c** should imply a pseudo-equatorial orientation of $^{t}$Bu group.

The allylation reaction depicted in Scheme 1 can be extended in a twofold manner. First, various substituents could replace the methyl linked to the double bond in **4a-c** and **5a-c**.[14] Second, numerous functions can be introduced in the 3-position by using other electrophilic reagents instead of aldehydes. Thus, the reaction of complex **2** with propionyl chloride, methyl chloroformate or dimethylcarbamoyl chloride afforded respectively ketone **6**, methyl ester **7** or amide **8** (Scheme 3). In each case only a single product was seen. Moreover, a simple protonolysis of the complex **2** gave rise to the formation of 10-methyl-β-pinene **9**.




Electrophile : EtCOCl , $ClCO_2Me$ , $ClCONMe_2$ , $H_3O^+$ ,

**Compound** (yield): E = **6** (45%): COEt ; **7** (48%): $CO_2Me$ ; **8** (38%): $CONMe_2$ ; **9** (52%): H

Scheme 3

In summary, the allyltitanation reaction has proved to be a short and regioselective way of preparing new 3,10-difunctionalized or 10-monofunctionalized β-pinene derivatives from the simple α-pinene precursors. The use of further electrophiles and α-pinene derived dienes will extend the scope of the reported procedure.

## Experimental Section

**Materials and Methods.** All manipulations were carried out under argon using vaccum line techniques. The solvents used were distilled under argon from sodium benzophenone ketyl. Nopadiene (**1**) was prepared by a reported procedure from (1R)-(-)-nopol.[8] Titanocene dichloride was prepared by a literature method.[15] All electrophilic reagents were purchased from Aldrich, and distilled under Ar prior to use. $^1H$ and $^{13}C$ NMR spectra were recorded at 200 or 500 and 50 MHz, respectively. Mass spectra were obtained by EI (70eV) or positive ion FAB MS technique employing thioglycerol as the matrix solvent. Gas chromatography (GC) was carried out on 30m x 0.25mm cooper column packed with methyl silicone with a flow rate of 1.6 mL/min. Column flash chromatography was performed on silica gel 60 (Merk).

**Representative Procedure for the Preparation of Pinenyl Carbinols 4 and 5.** Isopropylmagnesium chloride (2 mL, 2M solution in THF) was added via syringe at r.t. to a stirred suspension of titanocene dichloride (1.00 g, 4.03 mmol) in 20 mL of THF. After 0.5 h the resulting green solution of $Cp_2TiCl$ was cooled to -20°C. A solution of i-PrMgCl in THF (2mL, 4 mmol) and nopadiene (4 mmol, ca. 0.6 mL) were added slowly and simultaneously by syringes. After stirring for 1 h the aldehyde was added neat, dropwise via syringe. The mixture was allowed to warm gradually to r.t. over a period of 1 h, and further stirred at this temperature for 1 h. The reaction mixture was poured into a separatory funnel containing 100 mL of ether, and treated with saturated aqueous $NaHCO_3$. (25 mL). The ether layer was separated and the aqueous layer was extracted with a second portion of ether. The combined organics were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was treated with ether/hexane = 1/1 (100 mL) and the titanium derivatives eliminated by filtration through a frit. The major portion of titanocene dichloride may be recovered by acidifying the aqueous layer. After concentration of the organic filtrate in vacuo, the isomers **4** and **5** were separated by flash chromatography (silica gel 230-400 mesh, hexane/ether 7:1 to 20:1 v/v). The yields and spectral data of **4a-c** and **5a-c** are as follows: **4a** (18.7%) IR (neat) 3470 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.32 (q, J=6.8 Hz, 1H), 3.25 (br dt, J=8.9, 5.4 Hz, 1H), 2.85 (dd, J=5.4, 5.4 Hz, 1H), 2.48 (s, 1H, $D_2O$ exanchgeable), 2.30-1.65 (m, 7H), 1.57 (dd, J=6.8, 0.7 Hz, 3H), 1.29 (d, J=10.2 Hz, 1H), 1.27 (s, 3H), 1.00 (t, 7.3 Hz, 3H), 0.70 (s, 3H), Z-alkene geometry deduced from +25% n.O.e for H-10 (hν C-1); $^{13}C$ NMR ($CDCl_3$) δ 142.2, 121.2, 76.9, 44.6, 43.0, 41.7, 41.2, 28.0, 26.0, 25.6, 21.2, 21.1, 12.7, 10.5; MS 208 ($M^+$, 5), 163 (100), 149 (75), 137 (20). **5a** (33.2%) IR (neat) 3380 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.38 (qd, J=7.0, 1.7 Hz, 1H), 3.88 (m, 1H), 2.83 (dd, J=5.4, 5.4 Hz, 1H), 2.60-2.46 (m, 1H), 2.37-2.20 (m, 1H), 2.00-1.83 (3H), 1.64-1.44 (m, 6H), 1.36 (s, 3H), 1.24 (d, J=9.5 Hz, 1H), 0.97 (t, J=7.3 Hz, 3H), 0.76 (s, 3H), Z-alkene geometry deduced from +24% n.O.e for H-10 (hν C-1); $^{13}C$ NMR ($CDCl_3$) δ 143.8, 116.9, 76.7, 44.3, 40.7, 40.4, 39.8, 28.5, 27.0, 26.5, 25.2, 21.8, 12.7, 11.0; MS 190 ($M^+$-18, 5), 175 (5), 150 (25), 119 (30), 107 (80), 91 (100). **4b** (29.7%) IR (neat) 3530 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.27 (q, J=6.6 Hz, 1H), 3.19 (ddd, J=9.5, 2.2, 2.0 Hz, 1H), 2.85 (dd, J=5.6, 5.6 Hz, 1H), 2.34-2.19 (m, 3H), 2.02-1.77 (m, 4H), 1.56 (dd, J=6.6, 0.9 Hz, 3H), 1.33 (d, J=10.2 Hz, 1H), 1.25 (s, 3H), 1.04 (d, J=6.8 Hz, 3H), 0.86 (d, J=6.8 Hz, 3H), 0.70 (s, 3H); $^{13}C$ NMR ($CDCl_3$) δ 142.6, 121.3, 79.4, 44.6, 41.8, 41.2, 40.4, 30.1, 28.4, 26.0, 25.4, 21.3, 21.2, 14.6, 12.7. **5b** (32.2%) IR (neat) 3470 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) δ 5.38 (qd, J= 6.9, 1.9 Hz, 1H), 3.48 (ddd, J=9.3, 3.1, 3.1

Hz, 1H), 2.84 (dd, J=5.7, 5.7 Hz, 1H), 2.79-2.66 (m, 1H), 2.45-2.25 (m, 1H), 2.00-1.75 (m, 4H), 1.65-1.61 (m, 1H), 1.57 (dd, J=6.5, 1.0 Hz, 3H), 1.26 (s, 3H), 1.23 (d, J=11.3 Hz, 1H), 1.03 (d, J=6.5 Hz, 3H), 0.89 (d, J=6.5 Hz, 3H), 0.77 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 141.4, 116.5, 80.7, 44.4, 40.7, 40.2, 37.3, 30.5, 28.8, 26.6, 25.0, 21.9, 20.2, 19.5, 12.7; MS 204 ($M^+$-18, 5), 161 (25), 150 (20), 119 (25), 107 (100). **4c** (46.5%) IR (neat) 3520 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.21 (q, J=6.7 Hz, 1H), 3.07 (dd, J=6.6, 2.2 Hz, 1H), 2.82 (dd, 5.4, 5.4 Hz, 1H), 2.47 (t, J=7.3 Hz, 1H), 2.31 (d, J=2.2 Hz, 1H, $D_2O$ exchangeable) 2.25 (dddd, J=10.3, 5.6, 5.6, 1.5 Hz, 1H), 2.14-1.88 (m, 1H), 1.61 (dd, J=6.8, 0.7 Hz, 1H), 1.58 (dd, J=6.8, 0.7 Hz, 3H), 1.41-1.32 (m, 2H), 1.26 (s, 3H), 0.90 (s, 9H), 0.71 (s, 3H); $^{13}$C NMR ($CDCl_3$) δ 143.5, 122.3, 83.9, 44.5, 41.9, 41.1, 38.6, 36.5, 33.5, 26.7, 26.0, 25.3, 21.3, 12.7; MS (GC-coupled) 236 ($M^+$, 5), 161 (10), 150 (35), 119 (30), 107 (100), 91 (85), 79 (80), 57 (75). **5c** (traces; not isolated; the ratio **5c/4c** ≤ 5/95 evaluated from $^1$H NMR and GC chromatography); MS (GC-coupled) 236 ($M^+$, 5), 161 (15), 150 (25), 119 (30), 107 (90), 91 (100), 79 (85), 57 (95).

**Reactions of Nopadiene-Derived Complex 2 with Propionyl Chloride, Methyl Chloroformate and Dimethylcarbamoyl Chloride : Ketone 6, Ester 7 and Amide 8.** The $\eta^3$-allyltitanium complex **8** was prepared as described above, starting from 4 mmol (1.00 g) of titanocene dichloride. The electrophilic reagent (4 mmol) was then added via syringe within a period of 10 min at -20°C. After stirring for 1-2 h at -20°C the reaction mixture was quenched with a saturated solution of $NaHCO_3$ and the workup was performed as outlined above. Separation by flash chromatography on a short silica gel column eluting with hexane/ether = 9/1 to 3/1 gave products: **6** (45%) IR (neat) 1715 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.39 (q, J=6.8 Hz, 1H), 3.25 (br d, J=9.5 Hz, 1H), 2.81 (dd, J=5.3, 5.3 Hz, 1H), 2.68-2.55 (m, 2H), 2.31-2.18 (m, 2H), 2.05-1.88 (m, 2H), 1.56 (dd, J=.6.8, 1.1 Hz, 3H), 1.25 (s, 3H), 1.24 (d, J=10.0 Hz, 1H), 1.03 (t, J=7.1 Hz, 3H), 0.71 (s, 3H), Z-alkene geometry deduced from +23% n.O.e for H-10 (hν C-1); $^{13}$C NMR ($CDCl_3$) δ 213.7, 139.8, 121.0, 50.2, 44.4, 41.2, 40.4, 34.4, 26.3, 26.2, 26.1, 22.0, 12.9, 7.9; MS : 206 ($M^+$, 10), 149 (65), 137 (55), 149 (45), 107 (90), 91 (100). **7** (42%): IR (neat) 1724 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.46 (br q, J=6.8 Hz, 1H), 3.66, (s, 3H), 3.33 (m, 1H), 2.82 (dd, J=5.4, 5.4, 1H), 2.33 (dddd, J=10.0, 5.8, 5.9, 1.5, 1H), 2.13 (m, 2H), 1.95 (m, 1H), 1.54 (d, J=10.0 Hz, 1H), 1.52 (br d, J=6.8 Hz, 3H), 1.26 (s, 3H), 0.71 (s, 3H), Z-alkene geometry deduced from +15% n.O.e for H-10 (hν C-1); $^{13}$C NMR ($CDCl_3$) δ 177.3, 138.6, 120.6, 52.3, 44.0, 41.4, 40.7, 40.1, 27.8, 27.0, 26.2, 21.5, 12.8; MS : 208 ($M^+$, 12), 194 (4), 149 (43), 107 (100). **8** (38%): IR (neat) 1640 cm$^{-1}$; $^1$H NMR ($CDCl_3$) δ 5.10 (qd, J=6.8, 1.4 Hz, 1H), 3.72-3.60 (m, 1H), 3.10 (s, 3H), 2.96 (s, 3H), 2.86 (dd, J=5.8, 5.8 Hz, 1H), 2.41-2.20 (m, 2H), 2.00-1.75 (m, 2H), 1.53 (dd, J=6.8, 1.4 Hz, 3H), 1.32 (d, J=9.2 Hz, 1H), 1.26 (s, 3H), 0.73 (s, 3H), Z-alkene geometry deduced from +10% n.O.e. for H-10 (hν C-1);$^{13}$NMR ($CDCl_3$) δ 177.6, 141.2, 118.9, 50.1, 44.1, 40.4, 37.9, 37.8, 36.1, 29.8, 27.6, 26.3, 21.7, 12.7; MS 221 ($M^+$, 30), 219 (100), 204 (15), 176 (30), 152 (45), 131 (25), 105 (25).

**Protonolysis of Complex 2 : 10-methyl-β-pinene (9).** The complex **2** (6 mmol in 25 mL THF) was obtained by the procedure outlined above. The protonolysis was performed at -20°C by adding the solution of dry HCl in THF (3.4 M, 1.8 mL). The mixture was then stirred for 15 min at r.t. The conventional basic ($NaHCO_3$) treatment and flash chromatography purification afforded **9** (52%), which had the spectral characteristics in accordance with the literature data.[16]

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