

Pinacol-Type Rearrangements of Intramolecular Photocycloadducts: Application of the 2,2-Dimethyl-4-Pentenoate Protecting Group

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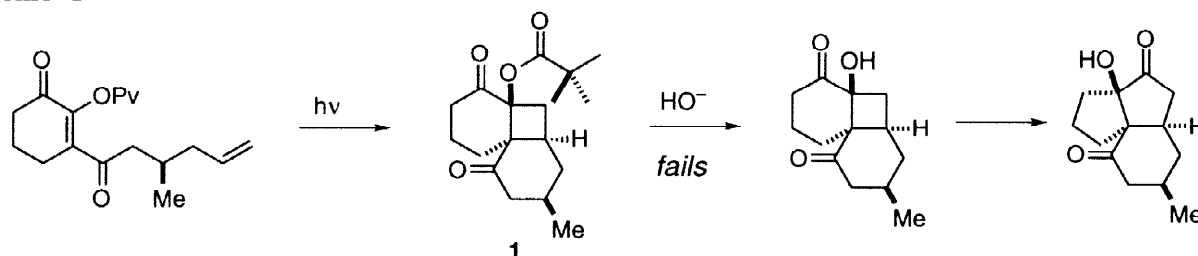
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Abstract: A pinacol-type rearrangement of intramolecular photocycloadducts has been accomplished by exploiting a novel ester protecting group that can be easily removed from a hindered alcohol. The ester is removed by an intramolecular lactonization, overcoming the steric factors normally associated with pivalate esters. © 1998 Elsevier Science Ltd. All rights reserved.

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The selective manipulation of functional groups in complex organic molecules often requires the use of protecting groups. While a variety of useful hydroxyl protecting groups are available,^{1,2} occasionally, a situation arises which cannot be resolved by existing protecting group technology. During the course of recent efforts directed toward the synthesis of the magellanane alkaloids, the intramolecular [2+2] photocycloaddition reaction of 2-pivaloxy enones was investigated.³ Removal of a tertiary pivalate from the photocycloaddition product **1** was required to effect the pinacol-type rearrangement of the [6-4-6] fused-ring system to the required [5-5-6] carbocyclic system. The difficulty encountered in the removal of the tertiary pivalate prompted the development of an alternative, novel protecting group, which would be more readily removed under mild conditions.

Scheme 1

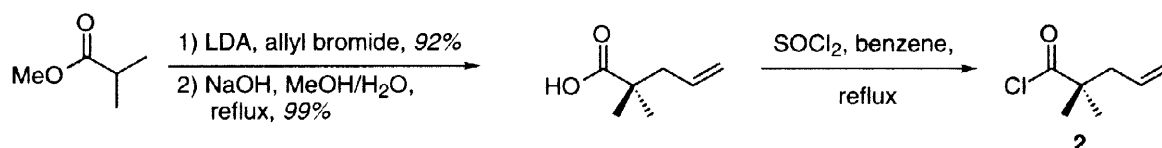


The ideal ester protecting group for this purpose would possess the following characteristics: 1) α -full substitution to preclude α -deprotonation under basic conditions, 2) photochemical stability, and 3) easy removal from a tertiary hydroxyl after the photocycloaddition reaction. The most efficient way to accomplish easy removal, considering the sterically hindered nature of the required ester group, was to design a protecting group that could

be removed by an intramolecular process, such as an internal lactonization, thus reducing the entropic and steric factors experienced in an intermolecular deprotection of such a sterically hindered ester. A suitable protecting group which met the above criteria was the 2,2-dimethyl-4-pentenoate (vinyl pivalate).

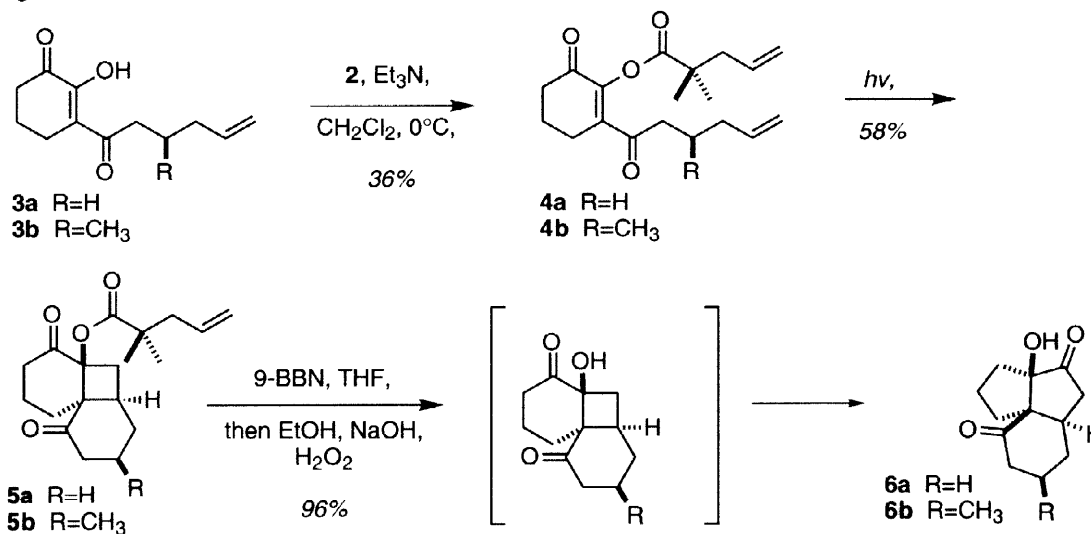
The synthesis of the vinyl pivalate is shown in Scheme 2. The enolate of methyl isobutyrate was alkylated with allyl bromide to form methyl 2,2-dimethyl-4-pentenoate which was then hydrolyzed to the acid under basic conditions. The dianion of isobutyric acid can also be alkylated with allyl bromide to afford the desired acid in a single-step process.⁴ Conversion of the acid to the acyl chloride proceeded smoothly by treatment with thionyl chloride in benzene at reflux.

Scheme 2



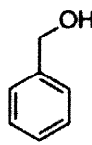
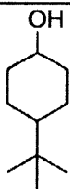
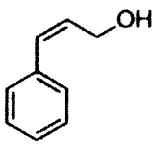
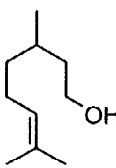
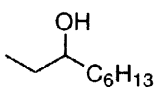
This acid chloride **2** was utilized in the acylation of enol **3** in a manner analogous to acylation with pivaloyl chloride (Scheme 3).³ The low yield for the protection of **3** can be attributed to the fact that both carbonyl groups are enolizable and multiple enol esters can be seen in the NMR spectrum of the unpurified product. Upon irradiation, enedione **4** was converted to the expected photoadduct **5**. Treatment of **5** with 9-borabicyclononane and subsequent oxidation under basic conditions⁵ successfully effected removal of the vinyl pivalate and rearrangement of the intermediate tertiary alcohol to the [5-5-6] skeleton **6**.

Scheme 3



To establish the generality of this novel protecting group, several simple alcohols were converted to their corresponding vinyl pivalates. The resulting vinyl pivalates were converted to the alcohols by hydroboration-oxidation of the olefin which resulted in spontaneous lactonization to effect cleavage of the ester. Deprotection by dihydroxylation with osmium tetroxide and 4-methylmorpholine *N*-oxide⁶ was successfully executed on the vinyl pivalates of two alcohols, dodecanol and 4-*t*-butylcyclohexanol (Table 1).

Table 1

	Alcohol	Protection	Deprotection		Alcohol	Protection	Deprotection
7		99%	72% (9-BBN)	10		88%	75% (OsO ₄)
8		99%	77% (9-BBN)	11		96%	64% (9-BBN)
9	$n\text{-C}_{11}\text{H}_{23}\text{OH}$	87%	87% (9-BBN) 77% (OsO ₄)	12		96%	96% (9-BBN)

In conclusion, a novel protecting group which can be removed either oxidatively or reductively as dictated by the sensitivity of the molecule in question has been developed. It has been exploited to effect a novel pinacol-type rearrangement of intramolecular photocycloadducts in high yield. The easy removal of the highly hindered vinyl pivalate should render it an attractive alternative to the pivalate and other ester protecting groups.

Preparation of 2,2-Dimethyl-4-pentenoic Acid: Method A: *n*-Butyllithium (101 mL, 0.162 mol) was added dropwise to a solution of diisopropylamine (16.35 g, 0.162 mol.) in 50 mL THF which had been precooled to -78°C . The resulting pale yellow solution was stirred 30 min. Methyl isobutyrate (15.00 g, 0.147 mol) in 50 mL THF was added dropwise over 30 min and the light yellow solution was stirred for an additional 1 h. Allyl bromide (19.54 g, 0.162 mol) in 50 mL THF was added dropwise and the solution was stirred for 1 h. Saturated NH_4Cl was added at -78°C to quench the reaction and the mixture was diluted with 100 mL ether. The organic layer was washed with brine and the combined aqueous layers were extracted twice with 100 mL ether. The combined organic layers were dried over MgSO_4 , filtered and concentrated *in vacuo*. Distillation of the residue yielded 19.23 g (92%) of methyl 2,2-dimethyl-4-pentenoate. The methyl ester (8.89 g, 0.063 mol) was dissolved in 400 mL methanol and 200 mL water. Sodium hydroxide (5.00 g, 0.125 mol) was added neat and the solution was heated to 80°C in an oil bath overnight. After cooling to room temperature, the methanol was removed *in vacuo*. The remaining aqueous layer was acidified with 10% H_2SO_4 and extracted with dichloromethane. The combined organic layers were dried over MgSO_4 , filtered, and concentrated, yielding 99% of 2,2-dimethyl-4-pentenoic acid (7.94 g, 0.062 mol).

Method B: Isobutyric acid (1.00 g, 11.35 mmol) in 10 mL THF was added dropwise to a suspension of NaH (510 mg, 12.75 mmol) in 20 mL of anhydrous THF and 1.35 g (1.75 mL, 12.48 mmol) of diisopropylamine. Once gas evolution was complete, the mixture was heated at reflux for 25 min. After cooling to 0°C , *n*-butyllithium (8.00 mL of 1.6 M hexane solution, 12.80 mmol) was added dropwise. The resulting mixture was stirred for an additional 25 min at 0°C and then warmed to room temperature for 2.5 h. Allyl bromide (685 mg, 5.67 mmol) was added dropwise at 0°C , the mixture was stirred for 1 h at 0°C and then warmed to 25°C for 12 h.

The mixture was then cooled to 0°C and 50 mL of water was added. The layers were separated, the aqueous layer was acidified with 10% HCl and then extracted three times with 50 mL ether. The combined extracts were washed with brine, dried over Na₂SO₄, and concentrated to afford 460 mg (3.56 mmol, 63.3%) of acid **1**.

Acid Chloride 2: Thionyl chloride (1.29 mL, 17.69 mmol) was added to a solution of acid **1** (1.50 g, 11.70 mmol) in 15 mL of benzene and the resulting mixture was heated to 80°C (oil bath) for 15 h. The solution was cooled to 25°C then carefully concentrated on a rotary evaporator to remove both the benzene and the excess thionyl chloride. Yields of **2** were quantitative as assayed by ¹H NMR.

General Procedure for Protection of Alcohols. The acyl chloride **2** (2.68 mmol) in 5 mL methylene chloride was added to a cooled (0°C) solution of alcohol **12** (0.28 mL, 1.79 mmol) and triethylamine (0.40 mL, 2.86 mmol) in 10 mL of dichloromethane. The mixture was warmed to 25°C and stirred for 15h. Saturated aqueous NaHCO₃ was then added to the reaction. The organic layer was dried over MgSO₄, filtered, and concentrated. The residue was purified by flash chromatography providing 0.412 g (1.714 mmol, 96%) of the ester.

General Procedure for Cleavage by Hydroboration. 9-BBN (1.5 mL, 1.5 mmol in THF) was added to a solution of the ester (1 mmol) in 10 mL THF and the mixture was stirred at 25°C for 6 h. After cooling to 0°C, 0.4 mL of ethanol and 1 mL of 6 N sodium hydroxide were added sequentially. The solution was stirred for 10 min and 2 mL of 30% hydrogen peroxide was added. The mixture was warmed to 25°C and stirred for 15h. After cooling to 0°C, saturated NaHCO₃ was added and the mixture was diluted with 15 mL ether. The layers were separated and the organic layer was washed with brine. The combined aqueous layers were extracted with 50 mL ether. The combined organic layers were dried over MgSO₄, filtered and concentrated. The residual oil was subjected to flash chromatography, yielding the purified alcohol.

General Procedure for Oxidative Cleavage: 4-methylmorpholine *N*-oxide (NMO) dihydrate (520 mg, 0.4416 mmol) and osmium tetroxide (0.17 mL of 0.04 M) were added to a solution of the vinyl pivalate of dodecanol in 16 mL acetone and 2 mL water. The mixture was stirred for 12 h, whereupon 5 mL of 10% sodium thiosulfate and 50 mL of ethyl acetate were added. The layers were separated and the organic layer was dried over MgSO₄, filtered and concentrated. The residue was purified by flash chromatography to provide 20 mg of dodecanol **9** (77% yield).

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References:

1. *Protective Groups in Organic Synthesis*. Greene, T.W.; Wuts, P.G.M., John Wiley and Sons, Inc. New York, 1991.
2. *Protecting Groups*. Kocienski, P.J., Georg Thieme Verlag, Stuttgart, 1994.
3. Crimmins, M.T.; King, B.W.; Watson, P.S.; Guise, L.E. *Tetrahedron* **1997**, *53*, 8963-8974.
4. Roth B.D.; Blankley, C.J.; Hoefle, M.L.; Holmes, A.; Roark, W.H.; Trivedi, B.K.; Essenburg, A.D.; Kieft, K.A.; Krause, B.R.; Stanfield, R.L. *J. Med. Chem.* **1992**, *35*, 1609-1617.
5. Brown, H.C.; Knights, E.F.; Scouten, C.G. *J. Am. Chem. Soc.* **1974**, *96*, 7765-7770.
6. VanRheenen, V.; Kelly, R.C.; Cha, D.Y. *Tetrahedron Lett.* **1976**, 1973-1976. Halterman, R.L.; McEvoy, M.A. *J. Am. Chem. Soc.* **1992**, *114*, 980-985.