Synlett I. B. Seiple et al. Letter

Practical Protocols for the Preparation of Highly Enantioenriched Silyl Ethers of (*R*)-3-Hydroxypentan-2-one, Building Blocks for the Synthesis of Macrolide Antibiotics

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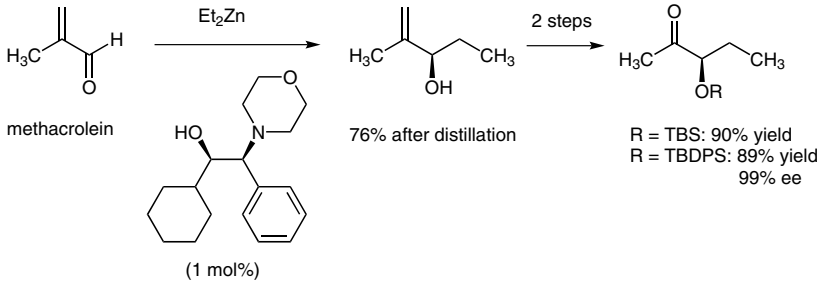
Dedicated with respect, admiration, and every good wish to Professor Steven V. Ley on the occasion of his 70th birthday



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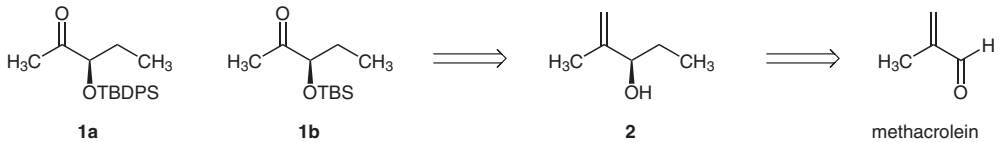
Abstract Methacrolein is transformed in three steps to (*R*)-3-*tert*-butyldiphenylsilyloxypentan-2-one or (*R*)-3-*tert*-butyldimethylsilyloxypentan-2-one, compounds which serve as building blocks for the construction of macrolide antibiotics. The route is practical, highly enantioselective, and easily scaled.

Key words enantioselective synthesis, macrolide antibiotics, asymmetric addition, organozinc reagent, Nugent protocol

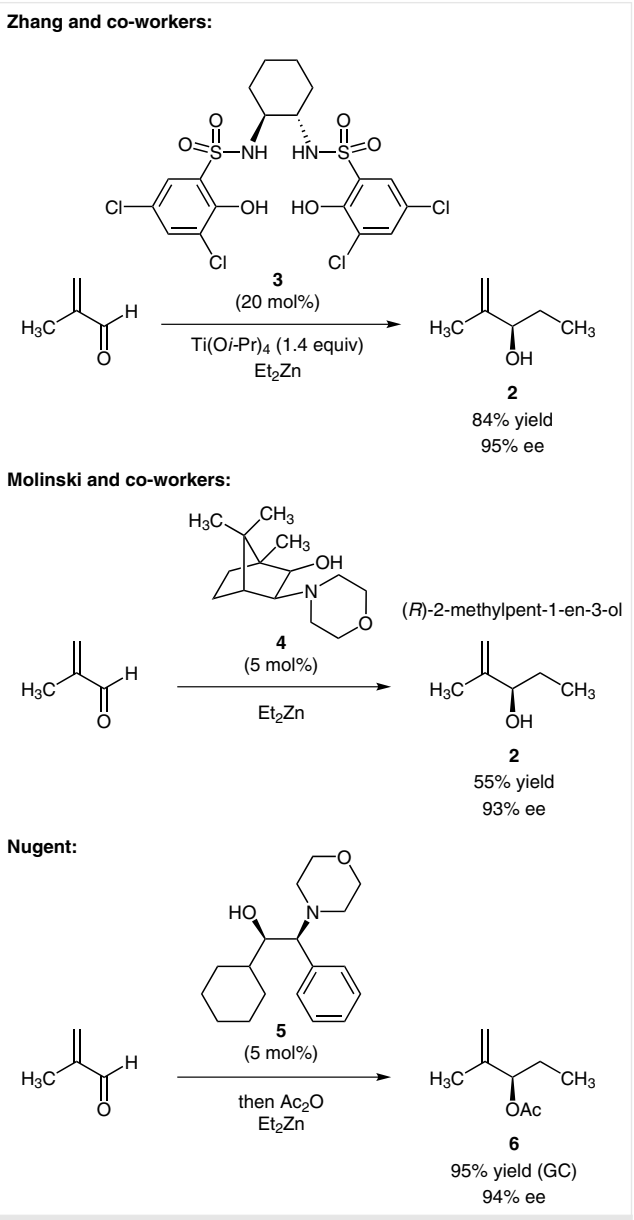
As a part of an ongoing effort to develop a practical, convergent platform for the synthesis of macrolide antibiotics in our laboratory, we required large quantities (10–100 g, with potential for further scaling) of (*R*)-3-*tert*-butyldiphenylsilyloxypentan-2-one (**1a**) as well as the corresponding 3-*tert*-butyldimethylsilyl ether (**1b**) as building blocks. We envisioned that both targets could be readily obtained from highly enantioenriched (*R*)-2-methylpent-1-en-3-ol (**2**), which in turn could be accessed from methacrolein (Scheme 1). Here we describe the successful realization of this plan and present practical laboratory procedures for the preparation of these useful chiral building blocks in quantity.

To the best of our knowledge, syntheses of enantiomerically enriched **1a** or **1b** have not been reported[1–3] and many of the published routes to access **2** in optically active form require kinetic resolution of a racemic substrate,[2–6] or proceed by multistep sequences.[7–9] Asymmetric addition of organozinc reagents to aldehydes in the presence of a chiral ligand provides a direct approach to access highly enantiomerically enriched secondary alcohols,[10–14] and three groups have prepared compound **2** in optically active form in this way, using methacrolein and diethylzinc as reactants (Scheme 2). Zhang and co-workers used 20 mol% of the chiral bis(sulfonamide) ligand **3** to promote the addition to provide allylic alcohol **2** in 95% ee and in 84% yield, but the need to use excess titanium(IV) isopropoxide (1.4 equiv) made this method less attractive for our purposes.[15] Molinski and co-workers used 5 mol% of the *N*-morpholinoisoborneol catalyst **4** (originally reported by Nugent)[16] to provide **2** in 93% ee and 55% yield.[17] Most promising, Nugent reported the use of the chiral β-amino alcohol **5** (5% loading) to catalyze highly enantioselective additions of diethylzinc to various aldehydes, including methacrolein.[18] While allylic alcohol **2** itself was not isolated, the corresponding acetate ester **6** was prepared in situ and shown to be of 94% ee. The ready availability and crystallinity of the catalyst **5** [prepared in 2 steps from (1*R*,2*S*)-(–)-2-amino-1,2-diphenylethanol, with no requirement for chromatographic purification] and the high efficiency of the addition (95% yield by gas chromatographic analysis after in situ acetylation) provided additional incentives for us to adopt Nugent's method for the synthesis of compound **2**. In the course of our explorations of this method, we have identi-



Scheme 1 Access to (*R*)-3-silyloxypentan-2-ones **1a** and **1b** from methacrolein through the intermediacy of allylic alcohol **2**

fied a number of procedural improvements that facilitate the addition protocol, reduce the catalyst loading, and minimize transfers of the pyrophoric reagent diethylzinc.

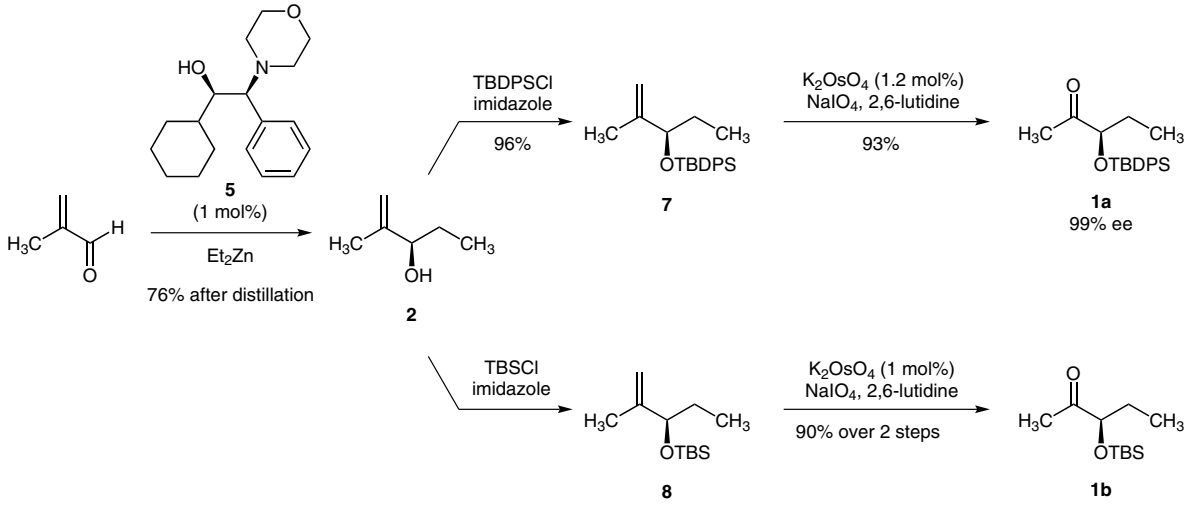


Scheme 2 Asymmetric additions of diethylzinc to methacrolein promoted by various chiral catalysts

Our revised protocol is as follows: diethylzinc solution (1.94 equiv, 1.0 M in hexanes) is added to a suspension of catalyst **5** (1 mol%) in dry hexanes in a round-bottom flask cooled with an ice–water bath. The resulting solution is allowed to stir for 30 minutes at 0 °C, and freshly distilled methacrolein (28 g, 1.0 equiv) is then added dropwise via a syringe pump over 90 minutes. After stirring for an additional 3.5 hours at 0 °C, an aqueous acidic work-up (ethyl ether–hydrochloric acid) allows for quantitative recovery of the catalyst **5** in high purity. The organic extracts are purified by distillation under reduced pressure, providing allylic alcohol **2** in 76% yield (31.4 g, bp 65–68 °C at 40 Torr) (Scheme 3). There are a number of notable differences between the general procedure reported by Nugent and our revised protocol. Nugent's procedure calls for addition of methacrolein and diethylzinc in hexanes–toluene (2:1) to dry catalyst **5**, whereas our procedure employs the addition of neat methacrolein to a pre-mixed solution of catalyst **5** and diethylzinc in hexanes (without toluene as a co-solvent). This order of addition may allow for formation of a catalyst–diethylzinc complex [**5**·$(Et_2Zn)_2$][13,14] prior to the addition of methacrolein, and serves to minimize the number of transfers of highly pyrophoric diethylzinc solution. Additionally, our protocol calls for lower catalyst loading (1 mol%) and is performed at a lower temperature (0 °C). Finally, we isolated the product **2** (by distillation), electing not to acetylate the intermediate zinc alkoxide as Nugent had. Our protocol has enabled the preparation of multigram quantities of allylic alcohol **2** in high enantiomeric purity (99% ee as determined by analysis of **1a**, as detailed below).[19]

The allylic alcohol **2** was used as the starting material for the synthesis of (*R*)-3-*tert*-butyldiphenylsilyloxypentan-2-one (**1a**) as well as the corresponding *tert*-butyldimethylsilyl ether (**1b**) by efficient two-step sequences (Scheme 3). To access **1a**, a solution of **2** (12 g) in *N*,*N*-dimethylformamide (1.0 M) was treated with imidazole (2.0 equiv) and *tert*-butyldiphenylsilyl chloride (1.3 equiv) at 23 °C. After extractive work-up and filtration through a pad of silica gel, silyl ether **7** was obtained in 96% yield. Oxidative cleavage of the carbon–carbon double bond within **7** was achieved by treatment with potassium osmate (1.2 mol%) and sodium periodate (4.0 equiv) in the presence of 2,6-lutidine (2.0 equiv).[20] We found that a reductive aqueous work-up (sodium thiosulfate solution) provided **1a** in sufficient purity for most subsequent transformations (38.6 g, 99% yield), but further purification could be achieved by simply passing a solution of the product in hexanes through a short plug of silica gel to provide the product as a light yellow oil (36.4 g, 93% yield). Ketone **1a** was shown to be of 99% ee by chiral HPLC analysis (Chiralcel OD-H column, hexanes eluent). An analogous sequence provided the *tert*-butyldimethylsilyl ether **1b** in 90% yield from **2**.[21]

In summary, we have developed a practical sequence to prepare the useful building blocks, (*R*)-3-*tert*-butyldiphenylsilyloxypentan-2-one (**1a**) and (*R*)-3-*tert*-butyldimethylsilyloxypentan-2-one (**1b**), of 99% ee and in approximately 68% yield from methacrolein, by simple modifications of Nugent's asymmetric addition protocol and straightforward protection and oxidation reactions. The reactions reported herein are efficient and practical, and have permitted us to prepare >100 gram quantities of **1a** and >20 gram quantities of **1b** as building blocks for use in the convergent syn-



Scheme 3 Synthesis of (*R*)-3-silyloxypentan-2-ones **1a** and **1b**

thesis of macrolide antibiotics. We believe this chemistry may be useful for other applications that require large quantities of various ethers of enantioenriched 3-hydroxypentan-2-one.

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560972.

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(19) **(*R*)-2-Methylpent-1-en-3-ol (2)**
A solution of Et_2Zn in hexanes (800 mL, 1.0 M, 800 mmol, 1.94 equiv) was added via cannula to an ice-cooled, stirring suspension of (1*R*,2*S*)-1-cyclohexyl-2-morpholino-2-phenylethanol (**5**) (1.24 g, 4.28 mmol, 0.01 equiv) in *n*-hexane (288 mL) in a 3 L round-bottom flask. White vapor formed in the receiving flask during the transfer. The resulting solution was allowed to stir for 30 min at 0 °C, then methacrolein (34 mL, 412 mmol, 1.0 equiv, freshly distilled) was added dropwise over 90 min using a syringe pump, producing a pale yellow, homogeneous solution. After 3 h, HCl (850 mL, 3 M) was added slowly (**Caution**: exotherm). A white precipitate was visible during the addition, but this redissolved toward the end of the addition (pH 1). The biphasic mixture was transferred to a separating funnel and the layers were separated. The aq layer was further extracted with Et_2O (2 × 500 mL), the organic layers were combined, and the resulting solution was washed with brine (500 mL). The washed solution was dried over Na_2SO_4 and filtered, and the filtrate was concentrated under reduced pressure (~40 Torr) at ≤10 °C. The resulting clear oil was transferred to a 250 mL round-bottom flask, and the transfer was quantitated with Et_2O (2 × 15 mL).

The solvent was removed at atmospheric pressure by distillation using a short-path distillation head, heating with a 90 °C oil bath. The heating bath was removed and the distillation flask was allowed to cool to 23 °C whereupon the pressure was carefully reduced to ~40 Torr. The receiving flask was immersed in an ice–water bath, and the distillation resumed upon heating with a 90–105 °C oil bath. The product distilled with a steady boiling point of 65–68 °C at ~40 Torr, providing allylic alcohol **2** as a colorless liquid (31.4 g, 76% yield). The enantiomeric excess was not determined at this stage, but was measured after conversion into **1a** (see the Supporting Information). The ^{1}H NMR and ^{13}C NMR data matched literature values.[5,2,22]

The acidic aqeous layers from the extraction were combined and the resulting solution was made basic with NaOH (~800 mL, 3 M) to pH 14, causing the precipitation of a white solid. The resulting suspension was extracted with CH_2Cl_2 (4 × 300 mL). The organic layers were combined and the resulting solution was dried over Na_2SO_4. The dried solution was filtered, and the filtrate concentrated to provide (1*R*,2*S*)-1-cyclohexyl-2-morpholino-2-phenylethanol (**5**) (1.19 g, 4.12 mmol, 96% recovery) in high purity.

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