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New Perspective for Natural Products Synthesis: Concise Synthesis of (+)-Sch 642305 by Chiral Auxiliary Multiuse Methodology

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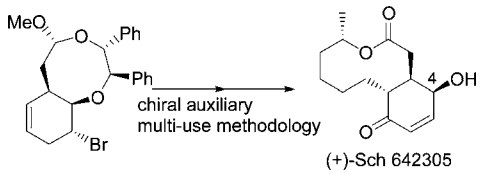
ABSTRACT



The synthesis of (+)-Sch 642305 is an example of chiral auxiliary multiuse methodology, which shows a new perspective for the synthesis of compounds with multiple asymmetric centers. Thus, (+)-Sch 642305 was concisely synthesized from the known compound. Every reaction is stereoselective, and the chiral nonracemic hydrobenzoin worked as chiral auxiliary for desymmetrization of diene, as a template for attaining regio- and stereoselective reactions, as an oxygen source at the C4-position, and as a protecting group of hydroxyl functions. Namely, the chiral auxiliary played a role in every step throughout the synthesis. Furthermore, the synthesis contains a new protocol for obtaining α′-alkylated enone compounds.

It is widely recognized that an enantioselective asymmetric synthesis with asymmetric catalysts is more efficient than the diastereoselective asymmetric synthesis with chiral auxiliaries, in which at least an equivalent amount of a chiral auxiliary is necessary. However, in the synthesis of complex molecules such as natural products, other factors such as regio-, stereo-, and chemoselectivity and protection and deprotection of functional groups must also be considered. Then, when we can use a single chiral auxiliary in controlling the reactions several times during the synthesis, even diastereoselective asymmetric synthesis becomes very efficient. The synthesis here is such an example and shows new perspective for the synthesis of the compounds with multiple asymmetric centers.

(+)-Sch 642305 (**1**) was first isolated from *Penicillium verrucosum* in 2003 by Schering-Plough scientists, Chu et al. It has been shown to be a potent inhibitor of bacterial DNA primase, DnaG, which is crucial for the replication of bacterial chromosomal DNA (an EC_{50} value of 70 μM).[1] In 2005, **1** was isolated from the fungus *Septfusidum* sp. by Merck scientists, Jayasuriya et al., and was shown to be a potent inhibitor of HIV-1 Tat transactivation (an IC_{50} value of 1 μM).[2] Since HIV-1 Tat is a regulatory protein required for viral replication, compounds inhibiting HIV-1 Tat show potential as a treatment of HIV infections. In addition to their unique structure, these promising biological profiles made (+)-Sch 642305 an attractive synthetic target for synthetic organic chemists. Four total syntheses[3−6] have been reported so far. The first three (refs 3−5) use long reaction schemes

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(1) Chu, M.; Mierzwa, R.; Xu, L.; He, L.; Terracciano, J.; Patel, M.; Gullo, V.; Black, T.; Zhao, W.; Chan, T.-M.; McPhail, A. T. *J. Nat. Prod.* **2003**, *66*, 1527−1530.

(2) Jayasuriya, H.; Zink, D. L.; Polishook, J. D.; Bills, G. F.; Dombrowski, A. W.; Genilloud, O.; Pelacz, F. F.; Herranz, L.; Quamina, D.; Lingham, R. B.; Danzeizem, R.; Graham, P. L.; Tomassini, J. E.; Singh, S. B. *Chem. Biodivers.* **2005**, *2*, 112−122.

(3) Mehta, G.; Shinde, H. M. *Chem. Commun.* **2005**, 3703−3705.

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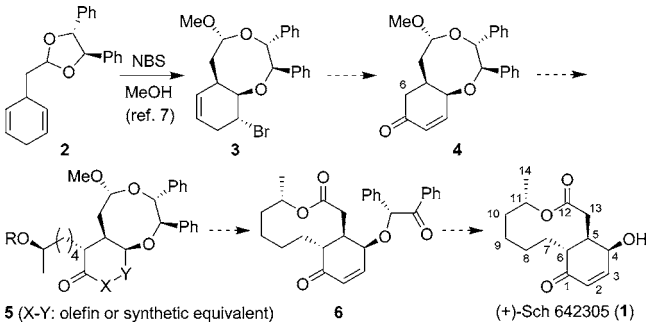
(17−19 steps). Although a quite recent report (ref 6) presents the very concise asymmetric synthesis of **1** in 12 steps, the starting material is the natural product, quinic acid. Then, an efficient and convergent approach to **1** remains highly desirable. We present here a concise asymmetric synthesis of **1** by chiral auxiliary multiuse methodology, in which the auxiliary works not only for asymmetric induction but also for regio- and stereoselective transformations and as a protecting group of hydroxyl functions.

The synthetic plan for (+)-Sch 642305 (**1**) is shown in Scheme 1. Our synthesis starts from the bromo acetal **3**,

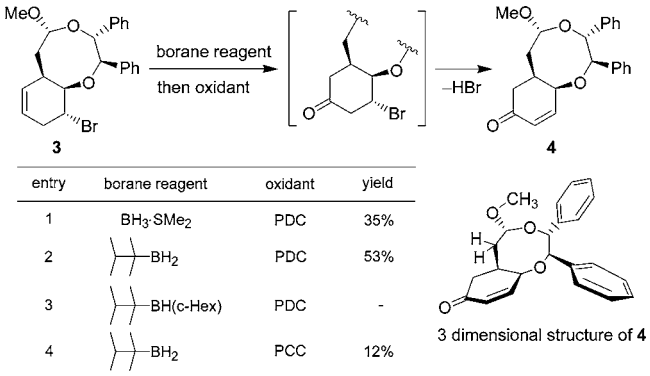
Scheme 1. Synthetic Plan for (+)-Sch 642305



which was previously synthesized by intramolecular bromoetherification of cyclohexadiene acetal **2**[7] and has convertible olefin and bromine moieties in the molecule. Furthermore, the 8-membered acetal moiety derived from the chiral auxiliary, (*R*,*R*)-hydrobenzoin, fixes the conformation of the cyclohexene ring promising high regio- and stereoselective transformations. Since several methods to remove the hydrobenzoin unit are available,[8] we planned to remove it at the final stage of the synthesis and hoped that the auxiliary would work not only as a protecting group of the alcohol part but also as a template for controlling the regio- and stereochemistry during the synthesis. We supposed the conversion of **3** to the enone **4** by regioselective hydroboration−oxidation at C1-position in the influence of the acetal ring. Introduction of a 6C unit at the α′-position (C6-position) of the enone **4**[9] was postulated to occur from α-side of the cyclohexane ring to give α-alkylated compound **5**, since its upper side is shielded by the 8-membered acetal ring. The olefinic part (X−Y) in **5** would be olefin itself or synthetic equivalent of olefin. Then **5** would be converted to the macrolactone **6** by the selective transformations. Final removal of 1,2-diphenylethylene unit would give (+)-Sch 642305 (**1**).

Conversion of the ene bromide **3** to the enone **4** was achieved by hydroboration−oxidation[10] (Scheme 2). Hydroboration of **3** followed by PDC oxidation gave the β-bromo ketone, from which spontaneous elimination of HBr occurred, giving the enone **4**. The use of BH_3·SMe_2 afforded the desired enone **4** in 35% yield (entry 1). The more bulky borane reagent, thexylborane, increased the yield (53%) of **4** (entry 2). However, the use of more bulky borane reagent, thexylborane cyclohexane complex, did not react at all (entry 3). The use of PCC in place of PDC decreased the yield of **4** (entry 4). The three-dimensional structure of **4** from its Dreiding model showed that the upper side of the cyclohexene ring is shielded by the axial C−C bond and the methylene group of the 8-membered acetal ring, which fixes the conformation.

Scheme 2. Conversion of **3** to the Enone Acetal **4**



entry	borane reagent	oxidant	yield
1	BH_3·SMe_2	PDC	35%
2	BH_2	PDC	53%
3	BH(c-Hex)	PDC	-
4	BH_2	PCC	12%

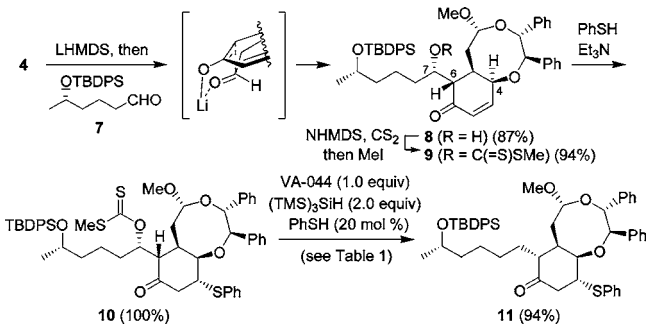
3 dimensional structure of **4**

Since direct alkylation at the α′-position of the enone **4** using a 6C-unit aliphatic trifluoromethane sulfonate or iodide failed, we attempted to introduce the 6C-unit by aldol reaction of aldehyde **7**.[11] Aldol reaction of **4** with **7** proceeded smoothly. As expected, it occurred from the sterically less hindered α-face of the cyclohexenone ring, and **8** was obtained as the diastereomerically pure form. The stereochemistry at the C6-position of **8** was deduced from mechanistic considerations and finally determined by an NOE experiment of xanthate **9**.[12] Although the stereochemistry of the secondary alcohol at the C7-position was not determined, it was tentatively deduced to be *S* by consideration of the 6-membered transition state.[13] Several trials for reducing the

(4) Ishigami, K.; Katsuta, R.; Watanabe, H. *Tetrahedron* **2006**, *62*, 2224−2230.
(5) Snider, B.; Zhou, J. *Org. Lett.* **2006**, *8*, 1283−1286.
(6) Wilson, E. M.; Trauner, D. *Org. Lett*. **2007**, *9*, 1327−1329.
(7) (a) Fujioka, H.; Kotoku, N.; Sawama, Y.; Nagatomi, Y.; Kita, Y. *Tetrahedron Lett.* **2002**, *43*, 4825−4828. (b) Fujioka, H.; Kotoku, N.; Sawama, Y.; Kitagawa, H.; Ohba, Y.; Wang, T.-L.; Nagatomi, Y.; Kita, Y. *Chem. Pharm. Bull.* **2005**, *53*, 952−957. We obtained **3** in 63% yield from **2** in ref 7a. In ref 7b, a similar compound, in which the MeO group of **3** is replaced by a $MeOCH_2$ group, was obtained in 57% yield. For the procedure to obtain **3**, see the Supporting Information.
(8) Oxidation of alcohol followed by reductive elimination: (a) Alexakis, A.; Trevitt, G. P.; Bermardinelli, G. *J. Am. Chem. Soc.* **2001**, *123*, 4358−4359. Oxidation of alcohol followed by Baeyer−Villigar reaction and methanolysis: (b) McNamara, J. M.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7371−7372. Birch reduction or hydrogenolysis: (c) Fujioka, H.; Kitagawa, H, Nagatomi, Y.; Kita, Y. *J. Org. Chem.* **2002**, *67*, 411−416. Using CAN: (e) Fujioka, H.; Hirose, H.; Ohba, Y.; Murai, K.; Nakahara, K.; Kita, Y. *Tetrahedron* **2007**, *63*, 638−643.
(9) The numbering is the same as that for (+)-Sch 642305 (**1**).
(10) Surendra U. K.; Herbert C. B. *J. Organomet. Chem.* **1979**, *172*, c20−c22.
(11) Yu, M.; Alonso-Galicia, M.; Sun, C-W.; Roman, R. J.; Ono, N.; Hirano, H.; Ishimoto, T.; Reddy, Y. K.; Katipally, K. R.; Reddy, K. M.; Gopal, V. R.; Yu, J.; Yakhi, M.; Frank, J. R. *Bioorg. Med. Chem.* **2003**, *11*, 2803−2821.
(12) NOE was observed between the C4-α-proton and the C7-proton in **9**.

secondary alcohol including radical reduction of the xanthate **9** in the presence of the enone unit were unsuccessful. This undesirable result might be due to the successive system of the enone unit and the γ-ether oxygen atom. The protocol, (1) conversion of the enone unit to the saturated one (masked enone), (2) radical reduction of the secondary alcohol, and (3) regeneration of the enone, was next examined. The masked enone method was accomplished by the use of the Michael addition of PhSH to the enone **9**. Thus, treatment of **9** with PhSH afforded β-sulfinyl ketone **10**, which was reduced with 2,2′-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (VA-044), the water-soluble radical initiator, and $(TMS)_3SiH$ in the presence of PhSH to afford the desired ketone **11**.[14] The configuration of the sulfinyl group was tentatively deduced to be *R* from the conformation of **9** (Scheme 3).

Scheme 3. Introduction of the 6C Unit



Radical reduction of **10** was a crucial step and studied in detail. The representative results are shown in Table 1. The most popular conditions for radical reduction of xanthates, AIBN-Bu_3SnH in dry benzene under reflux, afforded a complex mixture (entry 1). On the other hand, the use of PhSH as an additive gave the desired product **11** in a fairly good yield (entry 2). We next tried to use the water-soluble radical initiators to search for a more efficient method.[15] The use of VA-044 as an initiator and $(TMS)_3SiH$ as a chain carrier in wet EtOH gave a much better result, 75% (entry 3).

Table 1. Radical Reduction of **10** to **11**

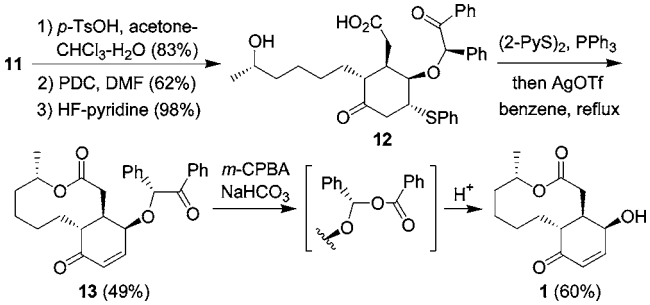
entry	initiator	chain carrier[c]	additive[d]	solvent, temp (°C)	yield (%)
1	AIBN[a]	Bu_3SnH		dry benzene, reflux	complex mixture
2	AIBN[a]	Bu_3SnH	PhSH	dry benzene, reflux	60
3	VA-044[b]	$(TMS)_3SiH$		wet EtOH,[e] 70	75
4	VA-044[b]	$(TMS)_3SiH$	PhSH	wet EtOH,[e] 70	94
5	VA-044[b]	$(TMS)_3SiH$	PhS−SPh	wet EtOH,[e] 70	90

[a] 0.2 equiv of AIBN was used. [b] 1.0 equiv of VA-044 was used. [c] 2.0 equiv of chain carriers was used. [d] 20 mol % of additive was used. [e] Contains ca. 0.5 vol % of water.

Addition of 20 mol % of PhSH improved the yield of **11** to 94% (entry 4). The use of PhS−SPh also showed the same reactivity (entry 5). The method here has several advantages: the use of nontoxic $(TMS)_3SiH$, a mild, efficient, and high yield reaction, and the use of wet EtOH.

Conversion of **11** to (+)-Sch 642305 (**1**) is shown in Scheme 4. Hydrolysis of the 8-membered acetal ring with *p*-TsOH followed by PDC oxidation and deprotection of TBDPS-ether with HF−pyridine afforded diketo carboxylic acid **12**. Macrolactonization using a modified Corey−Nicolaou method[16] gave the 10-membered lactone **13**. During the macrolactonization process, β-elimination of PhSH occurred together to regenerate the enone unit. Finally, *m*-CPBA oxidation of **13** caused the removal of the chiral source via the ester intermediate, which was labile and not isolated, to give (+)-Sch 642305 (**1**).

Scheme 4. Completion of the Synthesis of (+)-Sch 642305



In conclusion, we have succeeded in a concise asymmetric synthesis of (+)-Sch 642305 (**1**) from the known compound **3**.[17] Every reaction is stereoselective, and the chiral nonracemic hydrobenzoin worked as chiral auxiliary for desymmetrization of diene, as template for attaining regio- and stereoselective reactions, as an oxygen source at C4-position, and as a protecting group of hydroxyl functions. Furthermore, our synthesis, the method for constructing the 10-membered lactone and 4-hydroxycyclohexenone of **1**, is completely different from the previously reported syntheses (refs 3−6). Therefore, the method described here would be useful for preparing new derivatives which cannot be synthesized by other methods. Furthermore, new radical reduction using nontoxic $(TMS)_3SiH$ in wet EtOH is a very valuable transformation to obtain the α′-alkylated enone compound.

(13) The formation of single isomer depends on the substrate **4**. The reaction of cyclohexenone with **7** afforded a 3:1 mixture of the aldol products.

(14) Cf. Kita, Y.; Matsugi, M. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, 2001; Vol. 1, pp 1−10.

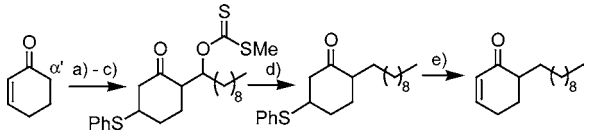
(15) For the effect of thiol in radical reduction, see: Cole, S. J.; Kirwan, J. N.; Roberts, B. P.; Willis, C. R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 103−112.

(16) Corey E. J.; Nicolaou K. C. *J. Am. Chem. Soc*. **1974**, *96*, 5614−5616.

(17) Although compound **2** was prepared from benzoic acid in four steps in our previous reports (ref 7), we improved its synthetic method and succeeded in getting **2** from commercially available cyclohexa-1,4-diene in two steps (see the Supporting Information).

Thus, the protocol for getting α′-alkylated enone compounds from enone compounds has generality (see ref 18). This transformation has two interesting aspects: a method for providing α′-alkylated enone compounds in good yields and a new method for radical reactions.

(18) Although the direct α′-alkylation of cyclohexenone with alkyl iodide or alkyl triflate under various conditions gave unsuccessful results, the protocol here [(a) aldol reaction, (b) xanthate formation, (c) conversion to the masked enone, (d) radical reduction, and (e) rebirth of the enone unit] gave the α′-alkylkated cyclohexenone in 55% overall yield.



a) LHMDS, decanal (93%); b) NHMDS, CS_2 then MeI (84%); c) PhSH, Et_3N (99%); d) VA-044, $(TMS)_3SiH$, PhSH, wet. EtOH (90%); e) *m*-CPBA, CH_2Cl_2 then in benzene, 80 °C (79%)

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Supporting Information Available: Full experimental details and detailed spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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