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A Practical Asymmetric Synthesis of *trans*-4,5-Benzhydrindan-1-ones as a Precursor of A-Nor B-Aromatic Steroidal Compounds

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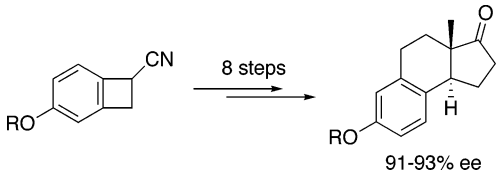

The enantio-controlled synthesis of *trans*-4,5-benzhydrindan-1-ones was achieved by means of a stereoselective [4+2] cycloaddition of *o*-quinodimethanes generated by a thermal cleavage of benzocyclobutene derivatives as a key step. The chiral substrates of the thermal reaction were synthesized by a diastereoselective Grignard addition to the chiral *O*-isopropylideneglyceroketones connected to a benzocyclobutene ring, which were simply prepared from D-mannitol as a chiral source. This approach can provide a new efficient access to A-nor B-aromatic steroidal compounds.

Introduction

trans-4,5-Benzhydrindan-1-ones consist of an A-nor B-aromatic steroidal skeleton, which are key intermediates for the synthesis of biologically important steroid-like compounds.[1] A difficulty in constructing the *trans*-fused C,D-ring system, however, has restricted available synthetic methods to a few reported examples, especially in an enantioselective fashion.[2] In a recent communication,[3] we have reported the synthesis of an optically active *trans*-4,5-benzhydrindan-1-one derivative based on the *o*-quinodimethane chemistry and its utility for the synthesis of a modified aglycon part of OSW-1, potent antitumor steroid saponin.[4] Although this preliminary study provided a new efficient approach to such a tricyclic system, it left some room for improvment for practical and large-quantity synthesis. In this context, we have succeeded in sharply saving the number of overall steps to increase the efficiency and the practicality of the method. In this paper, we describe a detailed account of this synthetic study.

Results and Discussion

Our continuous research on the *o*-quinodimethane chemistry using thermal cleavage of benzocyclobutene derivatives has revealed that subsequent intramolecular [4+2] cycloaddition works well for constructing the steroidal and steroid-like skeletons with high generality and stereoselectivity, including formation of the C,D-ring system having a trans relative configuration.[1] However, our previous studies for enantioselective synthesis of *trans*-4,5-benzhydrindans employing several chiral substrates ended in disappointing results, although satisfactory trans stereoselectivity was observed.[2b,c] To achieve an efficient and practical synthesis of optically active A-nor steroidal compounds, we designed new chiral substrates **3** possessing a dimethyl-1,3-dioxolane moiety, whose bulkiness would restrict the transition state of the cycloaddition to an exo-type one (leading to the trans stereochemistry) concomitant with the desired facial selectivity (Scheme 1). We planned to synthesize substrates **3** from chiral ketones **2** via a 1,2-asymmetric induction process. The key stages for this strategy are (1) preparation of compounds **2** from readily available benzocyclobutene **1**,[5] (2) diastereoselective nucleophilic

(1) Nemoto, H.; Fukumoto, K. *Tetrahedron* **1998**, *54*, 5425−5464 and references therein.

(2) (a) Ravindranathan, T.; Chavan, S. P.; Patil, S. S.; Pai, G. *Tetrahedron Lett*. **2002**, *43*, 1889−1891. (b) Nemoto, H.; Nagai, M.; Kohzuki, K.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1988**, 2835−2838. (c) Nemoto, H.; Matsuhashi, N.; Satoh, A.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 495−498. For classical synthesis of the racemates see: (d) Bachmann, W. E.; Thomas, D. G. *J. Am. Chem. Soc*. **1942**, *64*, 94−97. For a successful enantioselective synthesis see: (e) Bondon, D.; Pietrasanta, Y.; Pucci, B. *J. Chem. Res.* (*S*) **1980**, 112−113.

(3) Matsuya, Y.; Itoh, T.; Nemoto, H. *Eur. J. Org. Chem*. **2003**, 2221−2224.

(4) Kubo, S.; Mimaki, Y.; Terao, M.; Sashida, Y.; Nikaido, T.; Ohmoto, T. *Phytochemistry* **1992**, *31*, 3969−3973.

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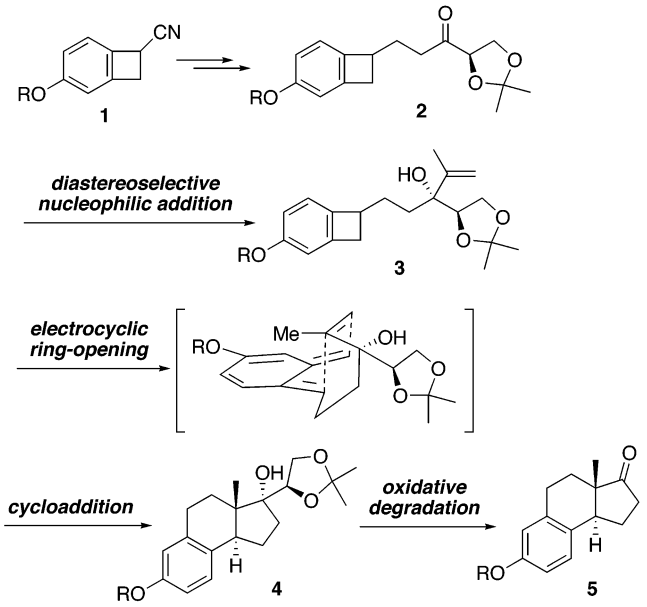
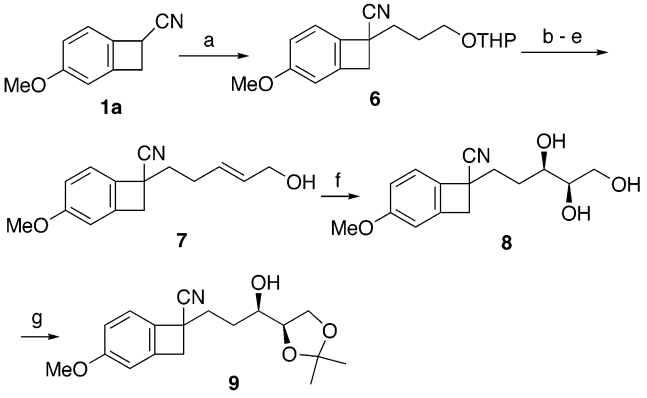
SCHEME 1



SCHEME 2[a]

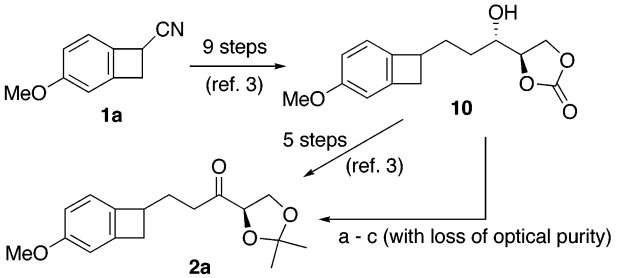


[a] Reagents and conditions: (a) LDA, THF, $Br(CH_2)_3OTHP$ (81%); (b) HCl, H_2O, MeOH; (c) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N; (d) NaH, $(EtO)_2P(=O)CH_2CO_2Et$, THF (42% in 3 steps); (e) DIBAL, Et_2O (63%); (f) $(DHQD)_2AQN$, *t*-BuOH, H_2O (87%); (g) MeOC(=CH_2)Me, HCl, DMF (22%).

addition to **2**, and (3) stereoselective pericyclic reaction of **3** and subsequent oxidative degradation.

1. Preparation of Chiral Ketones 2. For the construction of a chiral center of compound **2**, Sharpless asymmetric dihydroxylation was first applied as shown in Scheme 2. 4-Methoxybenzocyclobutene-1-carbonitrile (**1a**)[5] was alkylated and subsequently deprotected in accordance with the reported procedure[6] to afford the alcohol, which was transformed into the homologated allylic alcohol **7** through an oxidation−olefination−reduction sequence.[6] Because a method to remove a cyano group on the benzocyclobutene ring had been established,[7] we hastened to try the asymmetric oxidation of compound **7** and acetonization. Although the Sharpless

SCHEME 3[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, CH_2Cl_2, Et_3N; (b) K_2CO_3, MeOH; (c) MeOC(=CH_2)Me, PPTS, CH_2Cl_2 (25% in 3 steps).

dihydroxylation with $(DHQD)_2AQN$ proceeded successfully, subsequent acetonization of the resulting triol **8**, unfortunately, provided only 22% yield of the desired acetonide **9**, and one of several other products was determined as a five-membered cyclic acetal isomer.[8]

Consequently we directed our attention to the Sharpless asymmetric epoxidation of the allylic alcohol, because a promising method for converting epoxy alcohols to five-membered cyclic carbonates had been reported.[9] This approach has already been described in our previous communication,[3] and briefly shown in Scheme 3. To transform compound **10** (95% ee)[10] to the target chiral ketone **2a**, we first tried a simple three-step transformation including Swern oxidation, alkaline carbonate cleavage, and acetonization. Although this provided the ketone **2a** in moderate yields, it was found that this transformation involved considerable loss of the optical purity, probably due to the susceptibility of the intermediary keto-carbonate under basic conditions.[11] Thus, we were compelled to employ a rather circuitous pathway (5 steps), namely, protection of the alcohol **10** as a silyl ether, reductive cleavage of the cyclic carbonate, acetonization of the resulting diol, desilylation, and TPAP oxidation.[3] This sequential transformation provided the target ketone **2a**, the optical purity of which was preserved completely.[12]

Although the study mentioned above brought about a successful synthesis of the chiral ketone **2a**, we explored a more efficient and fewer step approach for the compounds. In a new plan, the chiral dimethyldioxolane subunit of **2** can be directly installed by using (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde, which is readily prepared from an inexpensive natural chiral source, D-mannitol.[13] As shown in Scheme 4, the cyano group in the starting benzocyclobutene **1a** was converted to the

(5) Kametani, T.; Kato, Y.; Honda, T.; Fukumoto, K. *J. Am. Chem. Soc.* **1976**, *98*, 8185−8190.

(6) Nemoto, H.; Satoh, A.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 943−946.

(7) Nemoto, H.; Nagai, M.; Abe, Y.; Moizumi, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1727−1733.

(8) While the product **9** afforded a corresponding ketone upon treatment with PDC, the isomeric side product gave an aldehyde by the same oxidation, which supported the structure determination of the acetonides.

(9) Roush, W. R.; Brown, R. J.; DiMare, M. *J. Org. Chem.* **1983**, *48*, 5083−5093.

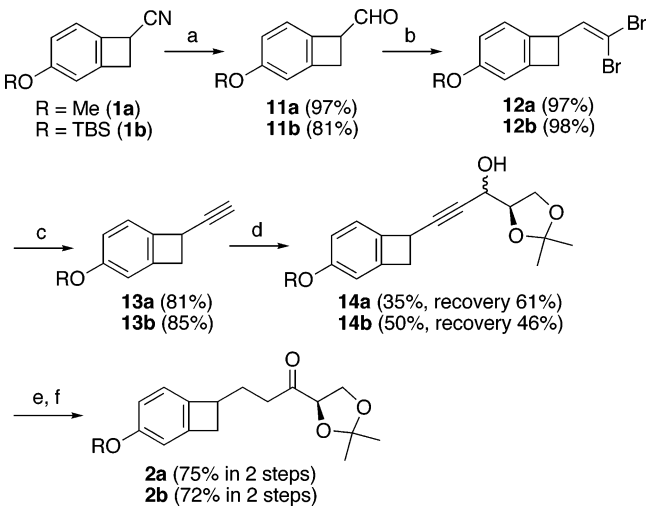
(10) The optical purity (95% ee) was estimated by the NMR spectra of the corresponding MTPA ester, and the absolute configuration was presumed from the empirical rule for the Sharpless asymmetric epoxidation. The diastereomers originating from a chiral center on the carbon bearing the cyano group were indistinguishable in the spectra.

(11) The product **2a** obtained from these manipulations was transformed into the final compound **5a**, which showed no optical rotation.

(12) The $[\alpha]_D$ value of the final compound **5a** synthesized from **2a** thus obtained was +93.5 (*c* 0.4, MeOH).

(13) Jackson, D. Y. *Synth. Commun.* **1988**, *18*, 337−341.

SCHEME 4[a]



[a] Reagents and conditions: (a) DIBAL, CH_2Cl_2; (b) PPh_3, CBr_4, CH_2Cl_2; (c) *n*-BuLi (2 equiv), THF; (d) *n*-BuLi (1 equiv), THF, (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde; (e) H_2, Pd/C, THF; (f) TPAP, NMO, MS4A, CH_2Cl_2.

formyl group by DIBAL reduction, and then alkynylation via dibromoalkene **12a** was performed. Lithiation of the resulting alkyne **13a** followed by exposure to (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde gave the alcohol **14a** as a mixture of diastereomers (ratio not determined) in 35% yield accompanied by a 61% yield of the starting alkyne,[14] which was recyclable without any loss (90% yield based on the consumed starting material). Of course, one-pot transformation of **12a** to **14a** by successive treatment with *n*-BuLi and the chiral aldehyde was also possible with a comparable yield. Hydrogenation of the triple bond and TPAP oxidation of the hydroxyl group proceeded in satisfactory yields to provide **2a**, which was confirmed to be identical with that synthesized in Scheme 3 with regard to the spectral and physical data. In addition, another derivative (**2b**) having an easily removable TBS group was synthesized from **1b** via the same pathway. Thus, a highly concise approach to the compounds **2** was established in 5 steps from **1**, in contrast to the required 14 steps in Scheme 3.

2. Diastereoselective Addition to Chiral Ketones 2. The next phase of the study was introduction of an isopropenyl group to the chiral ketones **2**, accompanied by 1,2-asymmetric induction. Precedent studies on the diastereoselective addition to analogous ketones, having the adjacent chiral dimethyldioxolane moiety, have revealed that the stereochemical course of the reaction is highly dependent on the counter metal of carbon nucleophiles and reaction conditions (solvent, temperature, additive, and so on).[15] However, only a few studies have been reported on this subject so far compared with the corresponding aldehyde (2,3-*O*-isopropylideneglyceraldehyde),[16] and recent reports have dealt with a particular substrate containing a chelatable dithioacetal[15b] or furan[15a] substructure adjacent to the carbonyl group, making the prediction of a suitable condition for our substrates **2** difficult. Therefore, several conditions were examined on nucleophilic addition of isopropenyl metal reagents to the chiral ketone **2a**, and a summary of the results is given in Table 1. When the ketone **2a** was exposed to 2-lithiopropene in THF at −78 °C, the adduct **3a** was obtained in a good yield; but disappointing stereoselectivity was observed with the predominant formation of undesired syn adduct (entry 1). The corresponding zinc reagent gave no adduct under the same condition (entry 2). On the other hand, gratifyingly, it was found that the requisite *anti*-**3a** was formed with a high diastereoselectivity by utilizing 2-propenylmagnesium bromide as a reagent (entry 3). A comparable result was obtained in less polar and non-Lewis basic solvent (toluene), and the selectivity was kept relatively high even at room temperature (entry 4−6), implying that the reaction course was controlled by a tight transition state including, presumably, α-chelation of the magnesium metal rather than the *β*-chelation or Felkin−Anh nonchelation model.[17] The TBS derivative **2b** was also subjected to the same reaction condition to afford *anti*-**3b** exclusively in a high yield (entry 7). Because available information on such exceptionally high stereoselectivity of the Grignard addition was quite limited from literature as mentioned above,[18] we felt a great interest in the generality of the reaction. Accordingly, the simple chiral ketones **15** and **16** were prepared[19] and subjected to the Grignard addition reaction under the optimized condition. This investigation revealed that high anti selectivity was realized in every case as shown in Scheme 5,[20] suggesting that these types of chiral ketones were versatile substrates for chiral syntheses through the 1,2-asymmetric induction process with a wide generality.

3. Thermal Transformation of 3 to A-Nor Steroidal Ketones 5. For the two substrates **3a** and **3b**, the key thermal reaction involved in the synthetic strategy was performed to achieve an efficient construction of the target A-nor C,D-trans steroidal skeleton in a highly stereoselective fashion (Scheme 6). The stereochemical course of the reaction should be directed by four possible transition states in the [4+2] cycloaddition step,[1] and the stereostructure of products **4a** and **4b** indicated that the reaction proceeded via the transition state presented in Scheme 1, because the others were much more congested due to the bulkiness of the dimethyldioxolane moiety. Compound **4a** was subjected to a one-pot transformation into ketone **5a** by treatment with periodic acid, including

(14) The corresponding zinc acetylide was prepared in situ to decrease the basicity of the reagent, and subsequent reaction with the aldehyde was examined, but ended in failure.

(15) (a) Tsubuki, M.; Tarumoto, N.; Honda, T. *Heterocycles* **2001**, *54*, 341−350. (b) Chikashita, H.; Nakamura, Y.; Uemura, H.; Itoh, K. *Chem. Lett*. **1992**, 439−442. (c) Chikashita, H.; Nikaya, T.; Uemura, H.; Itoh, K. *Bull. Chem. Soc. Jpn*. **1989**, *62*, 2121−2123. (d) Hagen, S.; Lwande, W.; Kilaas, L.; Anthonsen, T. *Tetrahedron* **1980**, *36*, 3101−3105. (e) Meric, R.; Vigneron, J.-P. *Bull. Soc. Chim.* Fr. **1973**, 327−330.

(16) Jurczak, J.; Pikul, S.; Bauer, T. *Tetrahedron* **1986**, *42*, 447−488 and references therein.

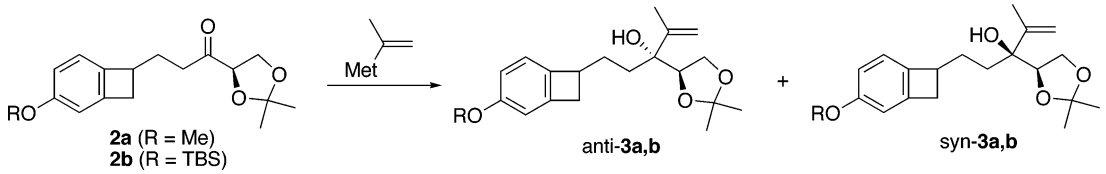
(17) Considerations of these reaction models are described in the previous papers: see refs 15a−c.

(18) With regard to a different trend of the stereoselectivity between the ketones utilized here and the corresponding aldehyde, higher Lewis basicity of the ketone carbonyl groups compared to that of the aldehyde may affect the stereochemical outcome.

(19) Preparative methods for compounds **15** and **16** are provided in the Supporting Information.

(20) Although the relative configurations of the adducts **17** and **18** were deduced on the basis of the empirical rule (Landmann, B.; Hoffmann, R. W. *Chem. Ber*. **1987**, *120*, 331−339), those of **3a** and **3b** were determined by NOE experiments after conversion to **4** (ref 3).

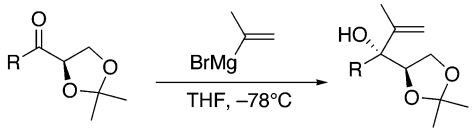
TABLE 1. Diastereoselective Addition of Isopropenyl Metal Reagents to Ketones 2



2a (R = Me)
2b (R = TBS)

entry	substrate	metal	solvent	temp (°C)	anti/syn	yield (%)
1	**2a**	Li	THF	−78	35/65	70
2	**2a**	ZnCl	THF	−78		0
3	**2a**	MgBr	THF	−78	95/5	90
4	**2a**	MgBr	toluene	−78	95/5	87
5	**2a**	MgBr	THF	rt	92/8	91
6	**2a**	MgBr	toluene	rt	85/15	87
7	**2b**	MgBr	THF	−78	100/0	93

SCHEME 5



R = *n*-C_6H_{13} (**15**)
R = Ph$(CH_2)_3$ (**16**)

17 (80% from **15**, anti / syn = 100 / 0)
18 (86% from **16**, anti / syn = 92 / 8)

acid-induced acetal cleavage and concurrent oxidative degradation. However, an HPLC analysis[21] of the resulting **5a** indicated relatively low enantiomeric excess (88% ee), which suggested that the cycloadduct **4a** contained a small amount of stereoisomer, presumably **4′**. Because we could not separate the isomer at this stage, compound **4a** was transiently converted to triol **22**, which could be purified by column chromatography to remove the isomer. The final ketone **5a** resulting from **22** showed an improved optical purity (93% ee), and the absolute configuration was determined based on the sign of the specific rotation.[2c] On the other hand, the TBS derivative **3b** afforded **4b** in a pure form, without any contamination of the stereoisomers. This compound was directly oxidized upon treatment with periodic acid to give the desilylated ketone **5c** in 52% yield (91% ee),[22] accompanied by **5b** (17% yield). The structure and the optical purity of product **5c** were determined after conversion to the known compound **5a** (MeI, K_2CO_3, DMF, quantitative yield). Thus, the synthesis of *trans*-4,5-benzhydrindan-1-ones **5a**−**c** was accomplished with high efficiency and high optical purity with use of *o*-quinodimethane chemistry.

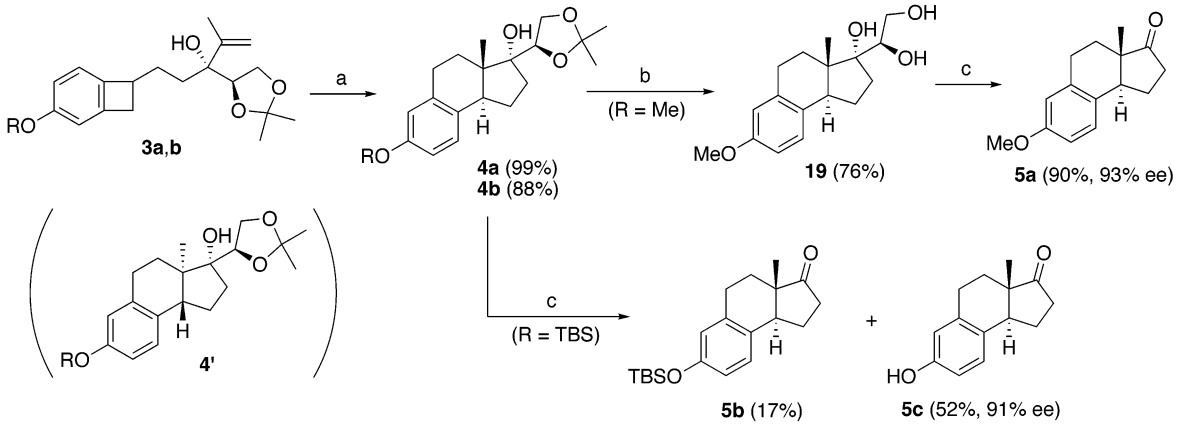
Conclusion

In this study, we have developed a new synthetic route to optically active *trans*-4,5-benzhydrindan-1-ones, which are useful substrates for syntheses of A-nor steroidal compounds. Through the described synthetic pathway, the target tricyclic ketones **5** were synthesized in 9 steps and 26−30% overall yield, starting from the benzocyclobutenes **1**. The simplicity and conciseness of the method described herein should provide a convenient access to various biologically important steroids. Further work on applying this methodology to the synthesis of several bioactive compounds is actively in progress in our laboratory.

Experimental Section

4-(*tert*-Butyldimethylsilyloxy)benzocyclobutene-1-carbonitrile (1b). 4-hydroxybenzocyclobutene-1-carbonitrile was prepared by demethylation of **1a**[5] according to the reported method.[23] To a solution of the hydroxybenzocyclobutene (1.10 g, 7.5 mmol) and triethylamine (1.26 mL, 9.1 mmol) in anhydrous CH_2Cl_2 (25 mL) was added TBSOTf (1.9 mL, 8.3 mmol) dropwise at 0 °C, and the mixture was stirred at room temperature for 1.5 h. The reaction mixture was diluted with 3% HCl aqueous solution and extracted with Et_2O, and the

SCHEME 6[a]



[a] Reagents and conditions: (a) *o*-dichlorobenzene, reflux; (b) *p*-TsOH, MeOH; (c) HIO_4, THF, H_2O.

organic layer was washed with saturated $NaHCO_3$ and brine, successively, and then dried over $MgSO_4$. The solvent was evaporated to leave a residue, which was chromatographed on silica gel (CH_2Cl_2) to give silyl ether **1b** (1.9 g, 97%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, J = 8.2 Hz, 1H), 6.77 (ddd, J = 8.2, 2.2, 1.0 Hz, 1H), 6.63 (d, J = 1.0 Hz, 1H), 4.15 (dd, J = 5.7, 2.8 Hz, 1H), 3.59 (dd, J = 14, 5.7 Hz, 1H), 3.46 (dd, J = 14, 2.8 Hz, 1H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 143.6, 131.1, 123.9, 121.0, 120.1, 115.5, 35.8, 28.2, 26.0, 18.5, −4.1; IR (neat) 2238 cm^{-1}; MS (EI) *m/z* 259 (M^+); HRMS (EI) calcd for $C_{15}H_{21}NOSi$ 259.1392 (M^+), found 259.1437.

4-(*tert*-Butyldimethylsilyloxy)benzocyclobutene-1-carbaldehyde (11b). To a solution of nitrile **1b** (4.0 g, 15.4 mmol) in anhydrous CH_2Cl_2 (45 mL) was added DIBAL (0.95 M in hexane, 19.4 mL, 19.0 mmol) at −78 °C, and the mixture was stirred at the same temperature for 0.5 h. After addition of saturated NH_4Cl solution, the aqueous mixture was vigorously stirred at room temperature for 0.5 h. The precipitates formed were filtered off through a Celite pad, and the filtrate was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated to leave a residue, which was chromatographed on silica gel (CH_2Cl_2) to afford aldehyde **11b** (3.3 g, 81%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.70 (d, J = 3.6 Hz, 1H), 7.01 (d, J = 7.9 Hz, 1H), 6.73 (dd, J = 7.9, 1.1 Hz, 1H), 6.66 (s, 1H), 4.15−4.12 (m, 1H), 3.38−3.34 (m, 2H), 0.98 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.1, 156.5, 145.0, 133.0, 124.3, 120.3, 115.5, 53.1, 30.4, 26.0, 18.5, −4.1; IR (neat) 1721 cm^{-1}; MS (EI) *m/z* 262 (M^+); HRMS (EI) calcd for $C_{15}H_{22}O_2Si$ 262.1389 (M^+), found 262.1400.

4-(*tert*-Butyldimethylsilyloxy)-1-(2,2-dibromoethenyl)-benzocyclobutene (12b). To a solution of triphenylphosphine (26.3 g, 97.5 mmol) in anhydrous CH_2Cl_2 (250 mL) was added tetrabromomethane (16.2 g, 48.8 mmol), and the resulting mixture was stirred at 0 °C for 0.5 h. A solution of aldehyde **11b** (2.56 g, 9.8 mmol) in anhydrous CH_2Cl_2 (20 mL) was added to the mixture, which was further stirred at room temperature. After 0.5 h, the reaction mixture was diluted with saturated $NaHCO_3$ and filtered through a Celite pad. The organic layer of the filtrate was separated and dried over $MgSO_4$, and then evaporated. The residue was subjected to column chromatography (CH_2Cl_2−hexane, 1:1) to afford the alkene **12b** (4.0 g, 98%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.95 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 8.0 Hz, 1H), 6.61 (d, J = 9.1 Hz, 1H), 6.59 (s, 1H), 4.23−4.18 (m, 1H), 3.50 (dd, J = 14, 5.5 Hz, 1H), 2.93 (d, J = 14 Hz, 1H), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 144.0, 140.3, 137.9, 123.6, 119.9, 115.2, 89.5, 44.9, 36.2, 26.0, 18.5, −4.1; IR (neat) 1594 cm^{-1}; MS (EI) *m/z* 415 (M^+); HRMS (EI) calcd for $C_{16}H_{22}Br_2OSi$ 415.9807 (M^+), found 415.9820.

4-(*tert*-Butyldimethylsilyloxy)-1-ethynylbenzocyclobutene (13b). A solution of alkene **12b** (143 mg, 0.34 mmol) in THF (3 mL) was cooled to −78 °C, and *n*-BuLi (1.6 M in hexane, 0.53 mL, 0.85 mmol) was added to the solution. After continuous stirring at the same temperature for 0.5 h, the reaction was quenched by addition of saturated NH_4Cl, and the aqueous mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated to leave a residue, which was chromatographed on silica gel (CH_2Cl_2−hexane, 1:2) to afford alkyne **13b** (76 mg, 85%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (d, J = 8.1 Hz, 1H), 6.71 (d, J = 8.1 Hz, 1H), 6.59 (s, 1H), 4.10 (dd, J = 5.0, 2.6 Hz, 1H), 3.51 (dd, J = 14, 5.0 Hz, 1H), 3.18 (d, J = 14 Hz, 1H), 2.27−2.25 (m, 1H), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 143.9, 136.8, 123.0, 120.0, 115.3, 84.8, 70.1, 37.9, 31.0, 25.9, 18.4, −4.1; IR (neat) 2120 cm^{-1}; MS (EI) *m/z* 258 (M^+); HRMS (EI) calcd for $C_{16}H_{22}OSi$ 258.1440 (M^+), found 258.1429.

(+)-4-(*tert*-Butyldimethylsilyloxy)-1-[3-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-1-propyn-1-yl]benzocyclobutene (14b). Method A: A solution of alkyne **13b** (52 mg, 0.2 mmol) in THF (3 mL) was cooled to −78 °C and treated with *n*-BuLi (1.6 M in hexane, 0.13 mL, 0.2 mmol) at the same temperature for 20 min. Then, a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (130 mg, 1 mmol) in THF (1 mL) was added to the mixture, and the resulting solution was stirred at −78 °C for 1 h. The reaction was quenched by addition of saturated NH_4Cl, and the aqueous mixture was extracted with CH_2Cl_2. After the solution was dried over $MgSO_4$, the solvent was evaporated to leave a residue, which was chromatographed on silica gel (CH_2Cl_2−AcOEt, 9:1) to afford alcohol **14b** (39 mg, 50%) as a colorless oil. The starting alkyne **13b** (24 mg, 46%) was also recovered. **Method B:** A solution of alkene **12b** (170 mg, 0.4 mmol) in THF (3 mL) was cooled to −78 °C, and *n*-BuLi (1.6 M in hexane, 0.53 mL, 0.85 mmol) was added to the solution. After 0.5 h, a solution of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (156 mg, 1.2 mmol) in THF (2 mL) was added. The same workup as in Method A gave **14b** (83 mg, 53%) and **13b** (34 mg, 32%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, J = 8.0 Hz, 1H), 6.70 (d, J = 8.0 Hz, 1H), 6.59 (s, 1H), 4.52−3.85 (m, 5H), 3.49 (dd, J = 14, 5.2 Hz, 1H), 3.15 (d, J = 14 Hz, 1H), 2.34 (br, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 143.9, 136.8, 136.7, 123.0, 120.0, 115.3, 110.5, 110.1, 87.3, 79.1, 79.0, 78.2, 66.4, 65.4, 64.8, 62.8, 38.0, 31.2, 31.1, 27.0, 26.6, 26.0, 25.6, 25.5, 18.4, −4.2; IR (neat) 3471, 2220 cm^{-1}; MS (EI) *m/z* 388 (M^+); HRMS (EI) calcd for $C_{22}H_{32}O_4Si$ 388.2070 (M^+), found 388.2075; $[\alpha]^{25}_D$ +15.3 (*c* 1.00, $CHCl_3$).

(+)-4-(*tert*-Butyldimethylsilyloxy)-1-[3-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-oxoprop-1-yl]benzocyclobutene (2b). A mixture of alkyne **14b** (694 mg, 1.8 mmol) and 10% Pd/C (80 mg) in THF (6 mL) was vigorously stirred under H_2 atmosphere at room temperature for 20 h. The catalyst was removed by filtration, and the filtrate was concentrated in vacuo to give the saturated product (620 mg, 88%) as an almost pure form. The product thus obtained (196 mg, 0.5 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL), and molecular sieves 4A (200 mg), NMO (117 mg, 1.0 mmol), and TPAP (18 mg, 0.05 mmol) were added successively. The resulting mixture was stirred at room temperature for 5 min, and then filtered through a Celite pad. The residue obtained by concentration of the filtrate was subjected to column chromatography (hexane−AcOEt, 3:1) to afford the ketone **2b** (166 mg, 83%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (dd, J = 8.0, 3.1 Hz, 1H), 6.64 (d, J = 8.0 Hz, 1H), 6.58 (s, 1H), 4.44−4.38 (m, 1H), 4.20−4.14 (m, 1H), 3.99−3.92 (m, 1H), 3.39−3.35 (m, 1H), 3.23 (dd, J = 14, 5.2 Hz, 1H), 2.74 (t, J = 7.4 Hz, 2H), 2.66 (d, J = 14 Hz, 1H), 2.04−1.87 (m, 2H), 1.48 (s, 3H), 1.39 (s, 3H), 0.98 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 155.3, 144.0, 140.8, 122.8, 118.9, 115.3, 110.9, 80.3, 66.6, 66.5, 41.7, 36.9, 36.8, 35.2, 27.8, 27.7, 26.2, 25.9, 25.2, 25.1, 18.3, −4.2; IR (neat) 1718 cm^{-1}; MS (EI) *m/z* 390 (M^+); HRMS (EI) calcd for $C_{22}H_{34}O_4Si$ 390.2226 (M^+), found 390.2182; $[\alpha]^{25}_D$ +31.1 (*c* 1.00, $CHCl_3$).

(+)-4-(*tert*-Butyldimethylsilyloxy)-1-[3-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-2-methyl-1-penten-5-yl]benzocyclobutene (3b). To a solution of ketone **2b** (146 mg, 0.4 mmol) in THF (10 mL) was added isopropenylmagnesium bromide (0.8 M in THF, 1.5 mL, 1.2 mmol) at −78 °C, and the reaction mixture was stirred at the same temperature for 1 h. The reaction was quenched with saturated NH_4Cl, and the aqueous solution was extracted with Et_2O and then dried over $MgSO_4$. Evaporation of the solvent gave a residue, which was chromatographed on silica gel (hexane−AcOEt, 3:1) to afford the alcohol *anti*-**3b** (149 mg, 93%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.89 (d, J = 7.9 Hz, 1H), 6.63 (d, J = 7.9

(21) The analytical condition for the determination of the optical purity of **5a** using HPLC has been described in ref 3.

(22) The optical purity of product **5c** (91% ee) was somewhat lower than expected. This may be attributed to a partial loss of the optical purity of (*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde used during the preparation or the reaction with the acetylide.

(23) Matsuya, Y.; Sasaki, K.; Nagaoka, M.; Kakuda, H.; Toyooka, N.; Imanishi, N.; Ochiai, H.; Nemoto, H. *J. Org. Chem.* **2004**, *69*, 7989−7993.

Hz, 1H), 6.57 (s, 1H), 5.10 (s, 1H), 5.02−5.00 (m, 1H), 4.31−4.25 (m, 1H), 4.04−3.95 (m, 2H), 3.31−3.29 (m, 1H), 3.22 (dd, J = 14, 3.2 Hz, 1H), 2.61 (dd, J = 14, 11 Hz, 1H), 1.95 (br, 1H), 1.77 (d, J = 7.1 Hz, 3H), 1.73−1.47 (m, 4H), 1.43 (s, 3H), 1.38 (s, 3H), 0.97 (s, 9H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.2, 146.5, 144.3, 122.7, 118.9, 115.4, 112.7, 109.2, 79.0, 76.5, 65.1, 42.6, 35.6, 35.4, 32.6, 28.3, 26.6, 26.0, 25.7, 20.2, 18.5, −4.1; IR (neat) 3565 cm^{-1}; MS (EI) *m/z* 432 (M^+); HRMS (EI) calcd for $C_{25}H_{40}O_4Si$ 432.2696 (M^+), found 432.2687; $[\alpha]^{25}_D$ +6.6 (*c* 1.00, $CHCl_3$).

(−)-7-(*tert*-Butyldimethylsilyloxy)-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-3-hydroxy-3a-methyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalene (4b). A solution of **3b** (35 mg, 0.08 mmol) in *o*-dichlorobenzene (5 mL) was refluxed for 5 h. Removal of the solvent left a residue, which was chromatographed on silica gel (CH_2Cl_2−AcOEt, 10:1) to afford cycloadduct **4b** (31 mg, 88%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.86 (d, J = 8.0 Hz, 1H), 6.61−6.58 (m, 2H), 4.36 (t, J = 7.2 Hz, 1H), 3.97−3.93 (m, 2H), 3.28−3.21 (m, 1H), 2.88−2.82 (m, 2H), 2.26−2.17 (m, 1H), 2.00−1.90 (m, 1H), 1.84−1.70 (m, 3H), 1.63−1.50 (m, 2H), 1.45 (s, 3H), 1.37 (s, 3H), 0.98 (s, 9H), 0.67 (s, 3H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.2, 137.3, 133.3, 126.9, 119.6, 117.1, 109.2, 81.5, 78.4, 65.6, 48.0, 45.5, 33.3, 29.0, 27.3, 26.8, 26.0, 25.5, 24.3, 18.5, 15.1, −4.1; IR (neat) 3565 cm^{-1}; MS (EI) *m/z* 432 (M^+); HRMS (EI) calcd for $C_{25}H_{40}O_4Si$ 432.2696 (M^+), found 432.2701; $[\alpha]^{25}_D$ −4.7 (*c* 0.81, $CHCl_3$).

(+)-7-(*tert*-Butyldimethylsilyloxy)-3a-methyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (5b) and (+)-7-Hydroxy-3a-methyl-1,2,3a,4,5,9b-hexahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (5c). To a solution of **4b** (40 mg, 0.09 mmol) in THF (3 mL) and H_2O (3 mL) was added periodic acid hydrate (105 mg, 0.46 mmol), and the mixture was stirred at room temperature for 22 h. After dilution with saturated $NaHCO_3$, the aqueous mixture was extracted with CH_2Cl_2 and then dried. The solvent was evaporated off, and the residue was subjected to silica gel column chromatography (CH_2Cl_2−AcOEt, 20:1) to afford **5b** (5.2 mg, 17%) and **5c** (11 mg, 52%) as colorless solids. **5b**: mp 87−89 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J = 7.7 Hz, 1H), 6.68−6.65 (m, 2H), 2.96−2.87 (m, 3H), 2.68−2.29 (m, 1H), 2.45−2.27 (m, 2H), 1.98−1.73 (m, 3H), 0.98 (s, 9H), 0.71 (s, 3H), 0.19 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 220.3, 154.0, 137.8, 130.7, 126.0, 120.1, 117.5, 48.2, 46.2, 36.8, 29.1, 26.8, 26.0, 21.7, 18.5, 14.3, −4.1; IR (KBr) 1738 cm^{-1}; MS (EI) *m/z* 330 (M^+); HRMS (EI) calcd for $C_{20}H_{30}O_2Si$ 330.2015 (M^+), found 330.1983; $[\alpha]^{25}_D$ +57.8 (*c* 0.55, $CHCl_3$). **5c**: mp 150−152 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99−6.96 (m, 1H), 6.69−6.59 (m, 2H), 5.02 (br, 1H), 2.95−2.86 (m, 3H), 2.72−2.61 (m, 1H), 2.46−2.27 (m, 2H), 1.98−1.73 (m, 3H), 0.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.5, 154.1, 138.0, 130.0, 126.2, 115.2, 112.8, 48.0, 45.9, 36.5, 28.7, 26.4, 21.4, 13.9; IR (KBr) 3400, 1718 cm^{-1}; MS (EI) *m/z* 216 (M^+); HRMS (EI) calcd for $C_{14}H_{16}O_2$ 216.1150 (M^+), found 216.1140; $[\alpha]^{25}_D$ +73.1 (*c* 0.53, $CHCl_3$).

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Supporting Information Available: Synthetic procedure and characterization data for the compounds **6**−**9**, **11a**−**14a**, and **15**−**18**, and NMR spectra of the compounds **2a**, **11a**−**14a**, **1b**−**5b**, **5c**, and **11b**−**14b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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