Total syntheses of (+)-castanospermine and (+)-6-epicastanospermine

Sung Ho Kang*† and Joon Seop Kim

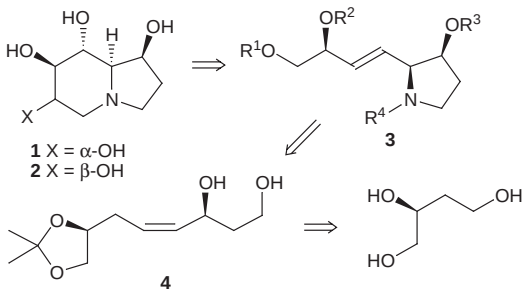
Department of Chemistry, Korea Advanced Institute of Science and Technology, Taejon 305-701, Korea

A divergent synthetic route to (+)-castanospermine 1 and (+)-6-epicastanospermine 2 has been developed *via* phenylselenoamidation of trichloroacetimidate derived from allylic alcohol 7, and dihydroxylations of *trans*-olefins 14 and 18 to dispose the three contiguous asymmetric centers, one amino group and two hydroxy groups.

The naturally occurring hydroxylated indolizidine alkaloids such as (−)-swainsonine, (+)-castanospermine **1** and (+)-6-epicastanospermine **2** continue to enjoy considerable attention from synthetic and medicinal chemists due to their pronounced biological activities. Their inhibition of enzymatic glycosidic hydrolysis is closely related with the potential chemotherapeutic utility for the treatment of diabetes,[1] cancer,[2] viral diseases[3] and AIDS.[4] Their intriguing molecular structures and promising medicinal value led us to explore their efficient synthetic routes. Here we describe total syntheses[5] of (+)-castanospermine **1** and (+)-6-epicastanospermine **2**, which have been isolated from *Castanospermum australe*[6] and *Alexa leiopetala*.[7]

Based on our retrosynthetic analysis toward **1** and **2**, a crucial synthetic step was a stereoselective dihydroxylation of *trans*-olefin **3** (Scheme 1). While the effect of the allylic amino group in **3** on the stereochemical outcome was in question,[8] its allylic alkoxy group was properly disposed for the desired α-dihydroxylation according to Kishi's empirical rule.[9] Another key step was to produce a *syn*-amino alcohol as a prospective precursor to **3** *via* intramolecular phenylselenoamidation of trichloroacetimidate derived from *cis*-olefinic allylic alcohol **4**.[10]

(*S*)-Butane-1,2,4-triol reacted with *p*-anisaldehyde in the presence of PPTS in benzene using a Dean–Stark trap to give a 7.5–8 : 1 mixture of 6- and 5-membered benzylidenes (Scheme 2). After Swern oxidation[11] of the inseparable mixture, the resulting aldehydes were olefinated with phosphonium salt **5** prepared from (*S*)-butane-1,2,4-triol[12] to afford a 19 : 1 mixture of *cis*-olefin **6**, $[\alpha]_D^{28}$ +110.8 (*c* 1.5, $CHCl_3$), and the corresponding *trans*-olefin in 69% combined overall yield, along with 7% of the isomeric olefins generated from the 5-membered benzylidenes. Hydrolysis of **6** with PPTS in MeOH at 0 °C removed its *p*-methoxybenzylidene group chemoselectively to provide diol **4**, $[\alpha]_D^{27}$ +9.9 (*c* 1.3, $CHCl_3$), in 86% yield. The primary hydroxy group of **4** was regioselectively silylated with TBDPSCl in the presence of imidazole at −60 °C to furnish silyl ether **7**, $[\alpha]_D^{22}$ −2.6 (*c* 2.2, $CHCl_3$), in 92% yield. For the unprecedent phenylselenoamidation, **7** was treated with

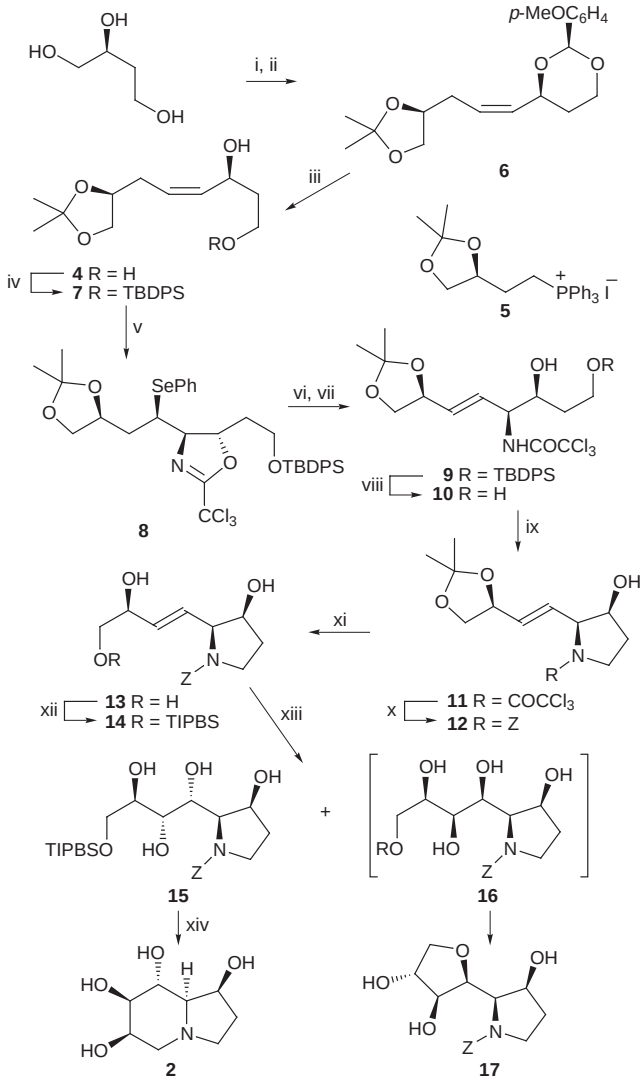


Scheme 1

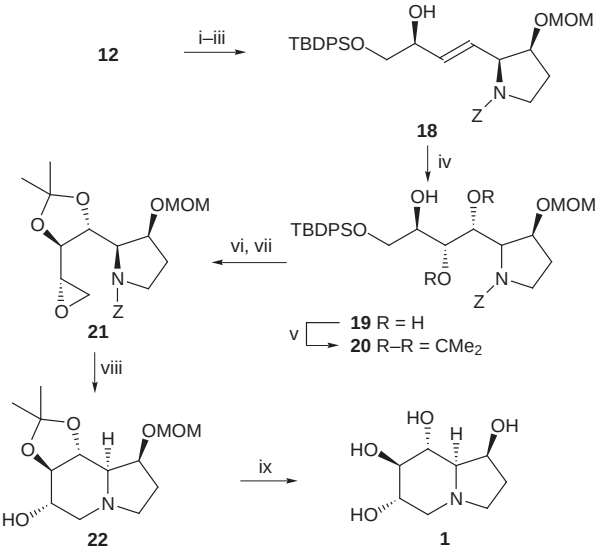
Cl_3CCN in the presence of DBU in MeCN at 0 °C, and subsequently cyclized using phenylselenyl chloride in the presence of methyl 2,2,2-trichloroacetimidate and Et_3N in MeCN at −20 °C to produce an inseparable 15 : 1 mixture of *trans*-oxazoline **8** and the isomeric *cis*-oxazoline in 63% combined yield. In this cyclization, the addition of methyl 2,2,2-trichloroacetimidate was essential to suppress the formation of the corresponding trichloroacetate from trichloroacetimidate. Subjection of the mixture to PPTS in aqueous MeOH induced partial hydrolysis of the oxazoline groups to give hydroxy trichloroacetamides, of which the desired *syn*-stereoisomer, $[\alpha]_D^{22}$ −6.8 (*c* 2.0, $CHCl_3$), was readily separated in 87% yield from the *anti*-stereoisomer. Oxidative elimination of the *syn*-stereoisomer with H_2O_2 in THF afforded *trans*-olefin **9**, $[\alpha]_D^{24}$ +15.8 (*c* 3.7, $CHCl_3$), in 84% yield contaminated with less than 3% of *cis*-isomer.

The next event was a stereoselective dihydroxylation of the introduced *trans*-olefinic double bond. In order to attain better stereoselectivity, **9** was variously functionalized by changing the protecting groups and the molecular structural shapes. It was found that the most promising outcomes could be obtained with benzyloxycarbonyl (Z)-protected pyrrolidine derivatives. Accordingly, **9** was desilylated in 92% yield and then the resultant alcohol **10**, $[\alpha]_D^{21}$ +34.9 (*c* 0.7, $CHCl_3$), was cyclized under Mitsunobu conditions[13] using diisopropyl azodicarboxylate (DIAD) and PPh_3 in THF at 0 °C to provide pyrrolidine **11**, $[\alpha]_D^{24}$ +58.6 (*c* 1.0, $CHCl_3$), in 88% yield. Treatment of **11** with BnONa in THF resulted in the formation of Z-protected pyrrolidine **12**, $[\alpha]_D^{26}$ +54.9 (*c* 1.1, $CHCl_3$), in 90% yield. After removal of the acetonide group under acidic conditions, the obtained triol **13**, $[\alpha]_D^{25}$ +17.0 (*c* 3.0, MeOH), was regioselectively sulfonated with 2,4,6-triisopropylbenzenesulfonyl chloride (TIPBSCl) in pyridine to furnish monosulfonate **14**, $[\alpha]_D^{25}$ +18.9 (*c* 1.2, $CHCl_3$), in 83% overall yield based on 15% of the recovered **13**. Dihydroxylation of **14** with a catalytic amount of OsO_4 in the presence of NMO in aqueous acetone[14] at 0 °C produced the requisite tetraol **15**, $[\alpha]_D^{23}$ +9.2 (*c* 1.1, $CHCl_3$), in 88% yield along with less than 8% of **17**, which was undoubtedly formed by the spontaneous intramolecular etherification of the isomeric tetraol **16**. Subjection of **15** to hydrogenolysis followed by *in situ* cyclization in the presence of Et_3N gave (+)-6-epicastanospermine **2**, $[\alpha]_D^{23}$ +2.8 (*c* 0.6, MeOH), in 66% yield.[15]

For the synthesis of (+)-castanospermine, **12** was converted into silyl ether **18**, $[\alpha]_D^{25}$ −12.6 (*c* 1.7, $CHCl_3$), in 88% overall yield by protection of the secondary hydroxy group with $MeOCH_2Cl$ (MOMCl), hydrolysis of the acetonide group and monosilylation of the primary hydroxy group with TBDPSCl in sequence (Scheme 3). Osmylation of **18** gave triol **19**, $[\alpha]_D^{24}$ −4.9 (*c* 0.7, $CHCl_3$), in 91% yield along with 6% of the isomeric β-dihydroxylated triol. When **19** was exposed to acetone in the presence of TsOH, the desired dioxolane **20**, $[\alpha]_D^{23}$ −7.1 (*c* 1.5, $CHCl_3$), was prepared in 92% yield by ketalization of the two *syn*-hydroxy groups, accompanied by 2% of the regioisomeric dioxolane. In order to secure the correct stereochemistry at 6-position of (+)-castanospermine, the remaining hydroxy group of **20** was inverted by mesylation followed by desilylation to afford epoxide **21**, $[\alpha]_D^{21}$ −19.7 (*c* 1.2, $CHCl_3$), in 87% overall yield. Removal of the Z group in **21**



Scheme 2 *Reagents and conditions*: i, *p*-anisaldehyde, PPTS, PhH, Dean–Stark trap; ii, $(COCl)_2$, DMSO, Et_3N, then **5**, Bu^nLi, HMPA, THF, −78 to 0 °C; iii, PPTS, MeOH, 0 °C; iv, TBDPSCl, imidazole, DMF, CH_2Cl_2, −60 °C; v, Cl_3CCN, DBU, MeCN, 0 °C, then PhSeCl, $MeOC(=NH)CCl_3$, Et_3N, MeCN, −20 to −15 °C; vi, PPTS, H_2O, MeOH, 20 °C; vii, 30% H_2O_2, THF, 0 to 20 °C; viii, Bu_4NF, THF, −5 to 0 °C, then aq. NaH_2PO_4; ix, DIAD, Ph_3P, THF, 0 °C; x, NaOBn, THF, 20 °C; xi, TsOH, MeOH, 20 °C; xii, TIPBSCl, pyridine, 20 °C; xiii, OsO_4, NMO, acetone, 0 °C; xiv, H_2, 10% Pd/C, MeOH, 20 °C, then Et_3N, reflux



Scheme 3 *Reagents and conditions*: i, MOMCl, Et_3N, CH_2Cl_2, reflux; ii, TsOH, MeOH, 20 °C; iii, TBDPSCl, imidazole, DMF, CH_2Cl_2, −60 °C; iv, OsO_4, NMO, H_2O, acetone, 0 °C; v, TsOH, acetone, 20 °C; vi, MsCl, DMAP, Et_3N, CH_2Cl_2, 20 °C; vii, Bu_4NF, THF, 20 °C, then 5 M NaOH; viii, 5% Pd/C, cyclohexene, EtOH, reflux; ix, conc. HCl, MeOH, reflux, then Dowex 50WX8-100 ion-exchange resin

was anticipated to induce 6-*endo* cyclization rather than 5-*exo* cyclization due to the *anti* arrangement of the dioxolane ring. Indeed heating **21** under catalytic transfer hydrogenation conditions[16] provided only indolizidine **22**, $[\alpha]_D^{22}$ +39.5 (*c* 0.8, $CHCl_3$), in 76% yield. Finally methanolysis of **22** with methanolic HCl furnished (+)-castanospermine **1**, mp 205–207 °C (decomp.), $[\alpha]_D^{22}$ +79.7 (*c* 1.0, MeOH), in 96% yield.[15]

In summary, we have accomplished total syntheses of (+)-castanospermine **1** and (+)-6-epicastanospermine **2**, which culminated in the stereoselective phenylselenoamidation of trichloroacetimidate (from **7**) and the asymmetric dihydroxylation of **14** and **18** to establish the four contiguous chiral centers.

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† E-mail: shkang@kaist.ac.kr

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