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Diastereocontrolled synthesis of an enantiopure 4,4-disubstituted cyclohex-2-en-ol: a new route to (+)-quebrachamine

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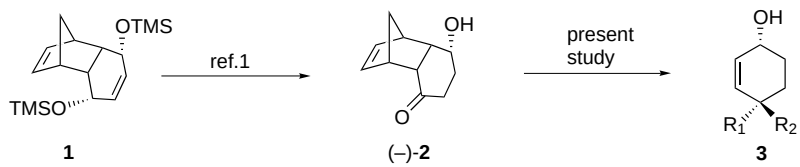
Abstract—A diastereoselective route to an enantiopure 4,4-disubstituted cyclohex-2-en-1-ol has been developed using the synthetic equivalent of chiral 4-hydroxycyclohex-2-en-1-one. Its stereochemistry has been determined by its transformation into the *Aspidosperma* indole alkaloid (+)-quebrachamine.

We have developed an efficient method for the preparation of the enantiopure tricyclic ketone **2**,[1] which serves as a synthetic equivalent of the chiral 4-ketocyclohex-2-en-1-ol **3** in both enantiomeric forms from the *meso* 2-ene-1,4-diol *bis*-silyl ether **1** using the Rh^{I}-chiral BINAP-mediated asymmetric 1,3-hydrogen transfer reaction.[2] Owing to its sterically biased framework allowing convex-face selective modification and its thermal lability to generate a cyclohexene double bond with extrusion of a cyclopentadiene molecule, the ketol **2** was used as the synthetic equivalent of the chiral 4-ketocyclohex-2-en-1-ol.[3] Because of its chemical and stereochemical nature, it has been utilized as a versatile chiral building block for the enantioselective synthesis of a variety of natural products by diastereocontrolled modification at the C2 and/or C3 centers of the cyclohexanol moiety.[4] However, a modification of its C4 center, namely construction of a quaternary center substituted by two carbon functionalities, was found to be very difficult and therefore prevented its utilization as a more versatile chiral building block. We report here a procedure for the diastereoselective construction of a quaternary stereogenic center on the C4-carbonyl center of the ketol (−)-**2** leading to the 4,4-disubstituted cyclohex-2-en-1-ol **3**, and the conversion of the product into (+)-quebrachamine,[5] the *Aspidosperma* indole alkaloid containing a quaternary stereogenic center. These findings confirm the stereochemistry of the newly introduced quaternary center as well as demonstrate its synthetic utility (Scheme 1).

Since the ketone (−)-**2** (>98% ee)[6] was somewhat unreactive toward organolithium or organomagnesium reagents as well as toward Wittig type reagents, presumably due to its facile enolization,[6] it was first treated with *N*-bromosuccinimide (NBS) to form the bromo–ether **4**,[1] mp 60–61°C, $[\alpha]_D^{29}$ −224.2 (*c* 0.5, $CHCl_3$), which has a more rigid framework. Although compound **4** was still not very reactive toward organometallic reagents, it did react with vinylmagnesium chloride in the presence of cerium(III) chloride[7] to give the tertiary allyl alcohol **5**, mp 120–121°C, $[\alpha]_D^{29}$ −108.0 (*c* 0.3, $CHCl_3$), diastereoselectively, in good yield. After considerable experimentation, the isomerization of **5** into an *E*/*Z*-mixture of the primary allyl alcohol **8** was carried out by employing a palladium-mediated reaction[8] of the tertiary allyl acetate **6** proceeding via an *E*/*Z*-mixture of the primary allyl acetate **7**. Thus, acetyl-



Scheme 1.

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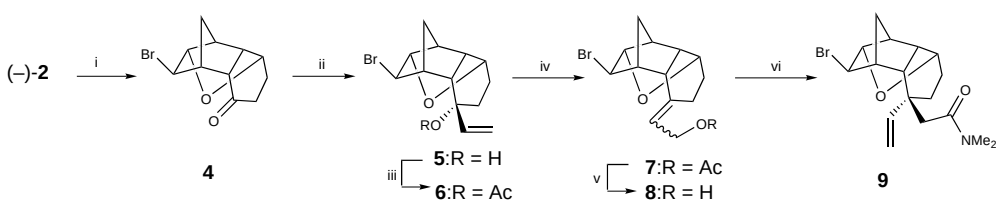
ation of **5** followed by treatment of the resulting tertiary acetate **6**, mp 124–125°C, $[\alpha]_D^{28}$ −163.5 (*c* 1.1, $CHCl_3$), with sodium acetate in the presence of dichlorobis(acetonitrile)palladium(II) in THF induced facile isomerization to furnish the primary acetate **7** as an inseparable *E*/*Z* mixture, from which the primary alcohol mixture **8** was obtained after alkaline methanolysis. Upon treatment with *N*,*N*-dimethylacetaminde dimethyl acetal[9] at 280°C in diphenyl ether, the primary alcohol mixture **8** furnished diastereoselectively the acetamide **9**, $[\alpha]_D^{28}$ −83.2 (*c* 0.7, $CHCl_3$), having a quaternary stereogenic center as the only product. Although the stereochemistry of the quaternary stereogenic center was not determined at this stage, it was assumed, on the basis of accumulated precedents,[4] that the Eschenmoser reaction of **8** should occur diastereoselectively to install the newly introduced functionality from the convex-face giving rise to the quaternary product **9** with an *endo*-vinyl functionality. This assumption was confirmed at a later stage (Scheme 2).

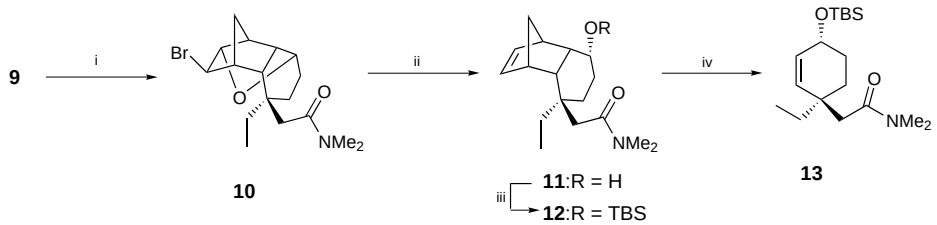
To unambiguously confirm its stereochemical pathway, as well as to demonstrate its synthetic utility, compound **9** was converted via the hydrogenated product **10** into (+)-quebrachamine **23**, an *Aspidosperma* indole alkaloid having a quaternary (*R*)-stereogenic center.[5] Thus, the vinyl-amide **9** was first hydrogenated on palladized charcoal to give the ethyl–amide **10**, mp 95–96°C, $[\alpha]_D^{29}$ −69.5 (*c* 1.6, $CHCl_3$). Upon exposure to zinc in methanol containing acetic acid,[4] compound **10** afforded the hydroxy–olefin **11**, mp 136–137°C, $[\alpha]_D^{31}$ −20.1 (*c* 1.0, $CHCl_3$), by reductive cleavage of its bromo–ether linkage with regeneration of the olefin and the secondary hydroxyl functionalities. Direct thermolysis of the secondary alcohol **11** in diphenyl ether at 280°C afforded the expected retro-Diels–Alder product in low yield accompanied by a complex mixture of by-products. However, thermolysis of its TBS ether **12**, $[\alpha]_D^{29}$ +9.6 (*c* 0.4, $CHCl_3$), in diphenyl ether at 280°C in the presence of sodium hydrogen carbonate[10] proceeded smoothly to give the expected cyclohexene **13**, $[\alpha]_D^{26}$ +81.4 (*c* 1.0, $CHCl_3$), in 93% yield. Although the effect of the sodium hydrogen carbonate is uncertain, when it is not used the reaction proceeds with considerable decomposition. This is particularly true when a hydroxyl functionality is present in the substrate (Scheme 3).

In order to obtain (+)-quebrachamine **23**, the amide **13** was first reduced with lithium triethylborohydride[11] to give the primary alcohol **14**, $[\alpha]_D^{27}$ +60.0 (*c* 0.9, $CHCl_3$), from which the silyl protective group was removed to give the diol **15**, $[\alpha]_D^{27}$ +69.9 (*c* 0.4, $CHCl_3$). Upon sequential ozonolysis, reduction with sodium borohydride, and glycol-cleavage with sodium periodate in the same flask, the diol **15** furnished the lactol **16** in 67% overall yield from the amide **13**. Oxidation of the lactol **16** with tetrapropylammonium perruthenate[12] (TPAP) afforded the formyl-lactone **18**, in one step as an unstable oil, which could also be obtained in comparable overall yield via the hydroxy–lactone **17**, $[\alpha]_D^{27}$ +2.7 (*c* 0.7, $CHCl_3$), by sequential Fetizon oxidation[13] and Swern oxidation.[14]

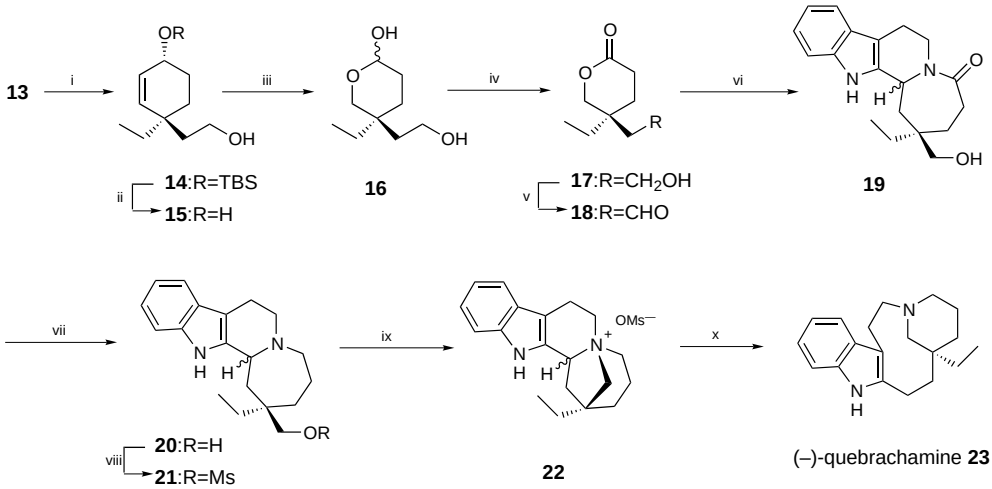
Condensation of the lactone **18** with tryptamine in benzene containing trifluoroacetic acid at reflux furnished the tetracyclic lactam **19** in one step as a mixture of two epimers by consective imine formation, intramolecular Pictet–Spengler reaction, and lactamization under the reaction conditions. The mixture was reduced with lithium aluminum hydride to give the tertiary amine mixture **20** the racemic mixture of which had been obtained[15] and ultimately transformed[15] into racemic quebrachamine (±)-**23**. Using the same procedure for the racemic synthesis, the mixture **20** was converted to the mesylate **21** which was immediately refluxed in chloroform to give the quaternary ammonium mesylate mixture **22**. Upon subjection to Birch reduction,[16] the mesylate mixture **22** furnished (+)-que-



Scheme 2. *Reagents and conditions*: (i) NBS, CH_2Cl_2, rt (99%); (ii) vinyl-Mg-Br, $CeCl_3$, THF, −78°C (87%); (iii) Ac_2O, pyridine, DMAP (cat.), rt (95%); (iv) $PdCl_2(MeCN)_2$ (cat.), THF, rt (100%); (v) K_2CO_3, MeOH, rt (98%); (vi) $MeC(NMe_2)(OMe)_2$, Ph_2O, reflux (96%).



Scheme 3. *Reagents and conditions*: (i) H_2, 10% Pd-C, AcOEt (92%); (ii) Zn, AcOH–MeOH (1:10), reflux (93%); (iii) TBS-Cl, imidazole, DMF, rt (94%); (iv) Ph_2O, $NaHCO_3$, reflux (93%).



Scheme 4. *Reagents and conditions*: (i) $LiEt_3BH$, THF, rt (84%); (ii) TBAF, THF (99%); (iii) O_3, MeOH, −78°C, then $NaBH_4$, then, $NaIO_4$, H_2O (67%); (iv) Ag_2CO_3–Celite, benzene, reflux (93%); (v) Swern oxidation; (vi) tryptamine, CF_3CO_2H, benzene, reflux (62%, two steps); (vii) $LiAlH_4$, dioxane, reflux (86%); (viii) Ms-Cl, pyridine, 0°C; (ix) $CHCl_3$, reflux; (x) Na, liq. NH_3, EtOH, −78°C (69% from **20**).

brachamine **23**, mp 147–149°C, $[\alpha]_D$ +106.1 (*c* 0.1, acetone){lit.[5a]: mp 147–149°C, $[\alpha]_D$ +108.9 (acetone)}, as a single product. The stereochemistry of the quaternary stereogenic center of the amide **9** as well as the stereochemical pathway of the Eschenmoser reaction of the allyl alcohol mixture **8** had thus been established unambiguously at this stage. The present synthesis implies development of a new diastereo- and enantiocontrolled route to both enantiomers of quebrachamine **23** since the starting ketone **2** may be obtained in both enantiomeric forms[1] (Scheme 4).

In conclusion, a method for enantio- and diastereocontrolled preparation of a 4,4-disubstituted cyclohex-2-en-1-ol using a synthetic equivalent of chiral 4-ketocyclohex-2-en-1-ol has been developed by employing the Eschenmoser reaction as the key step. Moreover, its stereochemical pathway has been verified by a new synthesis of the *Aspidosperma* indole alkaloid (+)-quebrachamine. Further research on the use of the enantiopure 4,4-disubstituted cyclohex-2-en-1-ols is in progress.

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