A Stereocontrolled Route to Cyclohexylethanoid Natural Products

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Abstract: Rengyol and seven related cyclohexylethanoid natural products have been synthesized in a stereocontrolled manner from a common starting material. In the present study the absolute configuration of the three chiral products has been determined and the first synthesis of a cyclohexylethanoid natural product bearing an oxetane ring has been accomplished.

In 1984, Endo and Hikino[1,2] first isolated rengyol **1** and rengyoxide **2** having a cyclohexylethano framework from the crude drug "rengyo", the fruits of *Forsythia suspensa* used in Oriental medicine for antiinflammatory, diuretic, drainage and antidotal purposes. Later, isorengyol **3** from the same plant[2,3] and a series of the structurally related cyclohexylethanoids, represented by isorengyol acetal **4**, cleroindicin A **5**, cleroindicin C (–)-**6**, cleroindicin E[4,5,6,7] (–)-**7** and isocleroindicin E[4] (–)-**8**, were isolated along with their glucosides from other medicinal plants, *Millingtonia hortensis*[4] and *Clerodendrum indicum*[5], both used in Southeast Asia (**Fig. 1**).

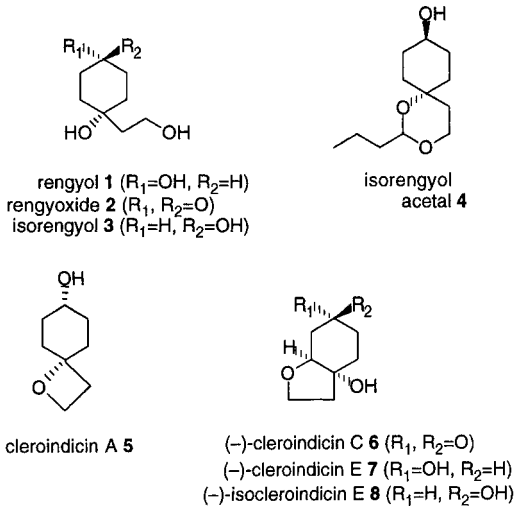


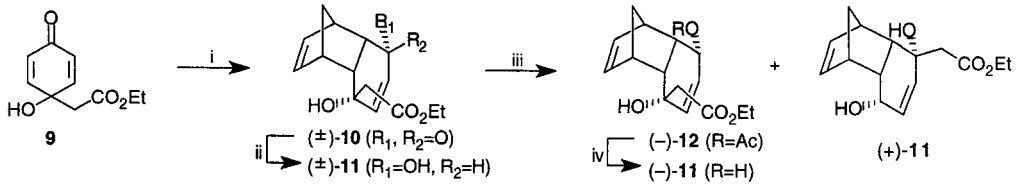
Figure 1

Because neither the synthesis nor determination of the absolute configurations has been made of the chiral natural products,[4,5,6] we were interested in developing a stereocontrolled route generally applicable to the construction of both the achiral and the chiral natural cyclohexylethanoids. We report here the stereocontrolled construction of these natural products **1** – **8** from a common starting material which determined the configuration of **5** having an oxetane ring and the absolute configurations of **6** – **8**.

The tricyclic enone **10**, mp 79-80 °C, obtained diastereoselectively[8] by the Lewis acid-mediated reaction of the dienone[9] **9** and cyclopentadiene, was used as the common starting material. 1,2-Reduction[10] of **10** occurred stereoselectively from the convex face to give the *endo*-alcohol (±)-**11**. Kinetic resolution of (±)-**11** occurred cleanly with vinyl acetate in the presence of Lipase LIP (Toyobo) in THF containing triethylamine[11] to give the acetate (–)-**12**, $[\alpha]_D^{33}$ –44.7 (*c* 0.7, $CHCl_3$), and the alcohol (+)-**11**, $[\alpha]_D^{32}$ +78.5 (*c* 1.1, $CHCl_3$), the former gave (–)-**11**, $[\alpha]_D^{29}$ –83.6 (*c* 1.4, $CHCl_3$), on alkaline ethanolysis. Enantiomeric purities of the products were estimated to be >99 and ~ 98% ee, respectively, by hplc analysis in the later stage (**Scheme 1**).

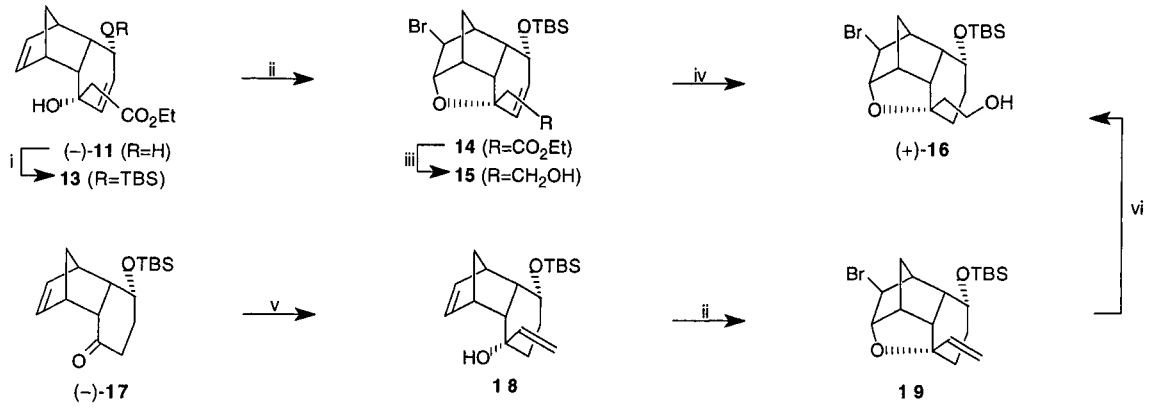
The absolute configurations of the products were determined as shown by correlation of (–)-**11** to the known ketone[12] (–)-**17**. Thus, (–)-**11** was transformed into the bromo-ether (+)-**16**, $[\alpha]_D^{31}$ +83.8 (*c* 0.1, $CHCl_3$), by a four-step sequence of reactions through **13**, **14** and **15**. On the other hand, (–)-**17** furnished the same bromo-ether (+)-**16**, $[\alpha]_D^{27}$ +79.9 (*c* 1.1, $CHCl_3$), in three steps through **18** and **19** (**Scheme 2**).

To establish an alternative route to the achiral natural products **1** – **3** as well as to accomplish the first synthesis of the achiral cleroindicin A **5** and to determine enantiomeric purities of the resolved products, the allyl alcohol (–)-**11** was first reverted to the enone (+)-**10**, mp 79-80 °C, $[\alpha]_D^{25}$ +92.7 (*c* 1.1, $CHCl_3$), by oxidation. The enone (+)-**10** was then transformed into the ketone **20** by a copper (I) iodide-mediated 1,4-reduction[13]. The readily enolizable ketone functionality of **20** was reduced with $NaBH_4$-$CeCl_3$[10] to give the *endo*-alcohol **21**, which, after silylation, was further reduced to give the diol **23**, $[\alpha]_D^{31}$ –6.8 (*c* 1.1, $CHCl_3$). On thermolysis in refluxing diphenyl ether, **23** furnished the cyclohexene (+)-**24**, mp 46-47 °C, $[\alpha]_D^{31}$ +38.9 (*c* 0.6, $CHCl_3$), whose enantiomeric purity was determined to be >99% ee by hplc analysis (CHIRALCEL OD, *i*PrOH-hexane 1 : 99) after conversion into the MTPA (*R*- and *S*-) esters. The enantiomeric cyclohexene (–)-**25**, mp 46-47 °C, $[\alpha]_D^{29}$ –36.3 (*c* 1.0, $CHCl_3$), obtained in the same way from the enantiomeric alcohol (+)-**11**, was determined to be ~ 98% ee. Hydrogenation of (+)-**24** gave the achiral cyclohexane **25** which, on desilylation, afforded rengyol[1,14] **1**, mp 120-122 °C (natural[1] : mp 124 °C). On the other hand, **25** was first transformed into the single acetal **26** which was desilylated to give **27**. The Mitsunobu reaction[15] of **27** yielded the inverted benzoate **28** which gave isorengyol acetal[4] **4** as the single product on alkaline methanolysis. Acid-catalyzed methanolysis



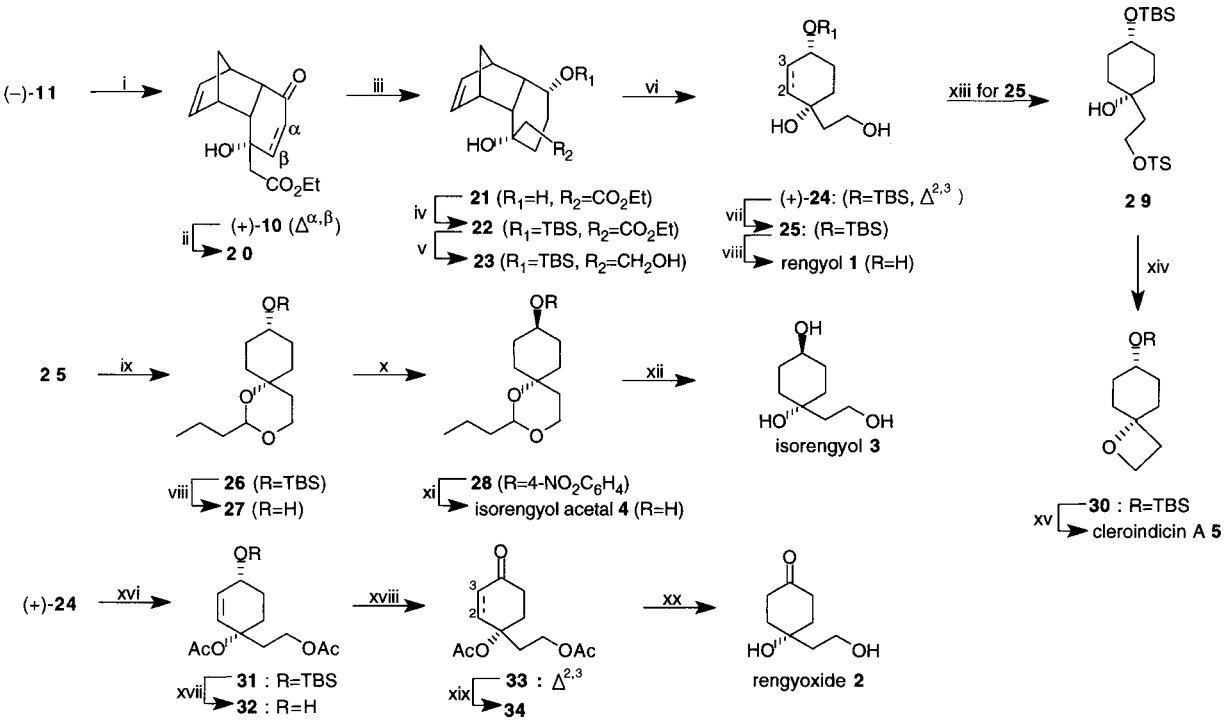
Reagents and conditions: i) cyclopentadiene, Et_2AlCl, CH_2Cl_2, –78 °C (89%). ii) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH (97%). iii) Lipase LIP, vinyl acetate, Et_3N, THF, 20 °C, 45h (44% for (–)-**12**; 50% for (+)-**11**). iv) DBU, EtOH, room temp., 40h (63%, 18% recovery)

Scheme 1



Reagents and conditions: i) TBSCl, imidazole, DMF, room temp. (89%). ii) NBS, CH_2Cl_2 (56% for **14**; 95% for **19**). iii) $LiBH_4$, THF (59%). iv) H_2, PtO_2, AcOEt (93%). v) vinylmagnesium bromide, THF (13%, 70% recovery). vi) $BH_3{\cdot}SMe_2$, THF then 30% H_2O_2, 2N NaOH (54%)

Scheme 2



Reagents and conditions: i) MnO_2, CH_2Cl_2 (96%). ii) DIBAL (1.5 M in toluene), CuI, HMPA, THF, –78 °C (98%). iii) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH (93%). iv) TBSCl, imidazole, DMF (98%). v) $LiBH_4$, THF (85%). vi) Ph_2O, $NaHCO_3$, 260 °C, 30 min (88%). vii) H_2, PtO_2, AcOEt (95%). viii) 48% HF, MeCN (99%) for **1**; 99% for **27**. ix) $PrCH(OMe)_2$, PPTS, CH_2Cl_2 (80%). x) $4\text{-}NO_2C_6H_4CO_2H$, diisopropyl azodicarboxylate, PPh_3, THF. xi) NaOMe, MeOH (40% from **28**). xii) PPTS, MeOH, reflux (81%). xiii) TsCl, Et_3N, CH_2Cl_2 (97%). xiv) Bu^{t}OK, DMF. xv) Bu_4NF, THF (91% from **29**). xvi) Ac_2O, DMAP, pyridine (94%). xvii) Bu_4NF, THF (93%). xviii) MnO_2, CH_2Cl_2 (100%). xix) H_2, 10% Pd-C, AcOEt (80%). xx) K_2CO_3, MeOH (68%)

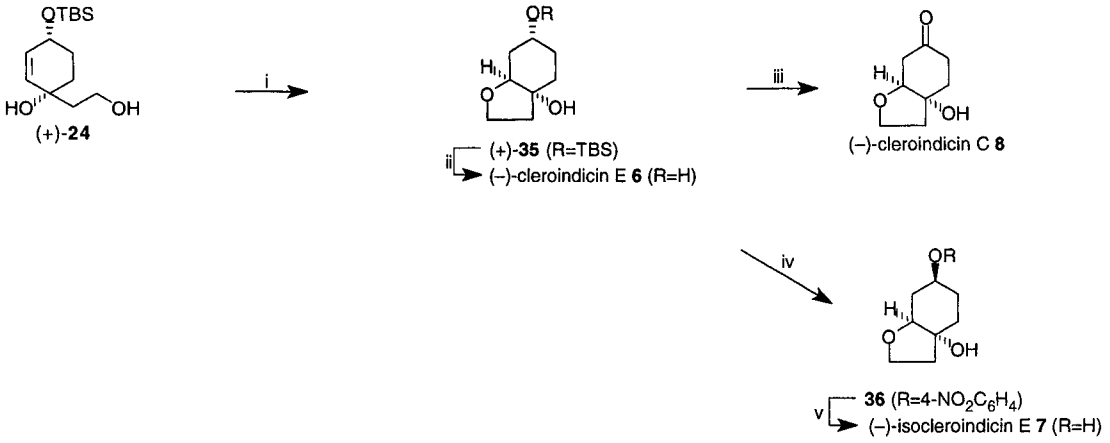
Scheme 3

of **4** afforded isorengyol[3,14] **3**, mp 106-108 °C (natural[3] : mp 107-108 °C).

In order to establish the configuration of cleroindicin A **5** having an oxetane ring on a unique spirobicyclic framework, the alcohol **25** was first transformed to the tosylate **29** which then was exposed to potassium *tert*-butoxide to furnish the bicyclic ether **30**. Finally, **30** was desilylated to give cleroindicin A **5** whose spectroscopic data (^1H and ^{13}C NMR, mass) were identical with those reported for the natural product.[5] Thus, the first synthesis of cleroindicin A **5** has been accomplished.

On the other hand, to obtain rengyoxide **2**, the cyclohexene (+)-**24** was first converted into the diacetate **31**. On sequential desilylation, oxidation, hydrogenation and alkaline methanolysis, **31** furnished rengyoxide **2** through the allyl alcohol **3**, the enone **33** and the ketone **34**. Of course, the synthesis of the compounds **1**–**5** may be carried out using the racemic adduct (±)-**10** without resolution as they are not chiral **(Scheme 3)**.

Having completed the synthesis of the achiral meso series of the natural products, we next examined the synthesis of the chiral natural products



Reagents and conditions: i) $(CF_3CO_2)_2Hg$, DME, then 5N NaOH, $NaBH_4$ (92%). ii) 48% HF, MeCN (98%). iii) PCC, CH_2Cl_2 (89%). iv) 4-$NO_2C_6H_4CO_2H$, diisopropyl azodicarboxylate, PPh_3, THF. v) NaOMe, MeOH (58% from **6**)

Scheme 4

6 – **8** to determine their absolute configurations. Thus, the cyclohexene (+)-**24** above was treated with mercury (II) trifluoroacetate[16] followed by sodium borohydride to form the bicyclic ether (+)-**35**, mp 40-41 °C, $[\alpha]_D^{28}$ +2.20 (*c* 1.2, $CHCl_3$), which served as the common precursor for the construction of the three chiral natural products, in 92% yield. Desilylation of (+)-**35** afforded cleroindicin E[4,5,14] (–)-**6**, mp 40-41 °C, $[\alpha]_D^{31}$ –5.96 (*c* 0.6, MeOH) [natural: $[\alpha]_D^{13}$ –2.6 (*c* 1.7, MeOH)[4], $[\alpha]_D$ +1.15 (*c* 0.046, MeOH)[5]]. On oxidation, (–)-**6** afforded cleroindicin C[4,5,14] **8**, $[\alpha]_D^{30}$ –71.0 (*c* 0.2, MeOH) [natural: $[\alpha]_D^{11}$ –5.6 (*c* 9.5, MeOH)[4]; $[\alpha]_D$ –22.32 (*c* 0.082, MeOH)[5]], while (–)-**6** on the Mitsunobu reaction[15] with 4-nitrobenzoic acid[17] followed by alkaline methanolysis of the resulted benzoate **36** furnished isocleroindicin E[4,14] (–)-**7**, $[\alpha]_D^{30}$ –22.6 (*c* 0.1, MeOH) [natural[4]: $[\alpha]_D^{16}$ –6.0 (*c* 0.57, MeOH)]. Based on the comparison of the direction of optical rotations, the absolute configurations of the three natural products have been determined as shown (**Scheme 4**). The observed discrepancies in the rotation values between the natural and the synthetic products may be due to a partial racemization of the former during their biosynthetic pathways involving quinonoid intermediates where racemization was presumed to occur by intramolecular elimination-addition pathway.[2,4]

In summary, we have devised a general and stereocontrolled procedure leading to both the achiral and the chiral cyclohexylethanoid natural products using a common starting material which determined the configuration of the one having meso structure and the absolute structures of the three having chirality.

References and Notes

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