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Enzymatic Resolution of Dioxygenated Dicyclopentadienes: Enantiopure Hydrindanes, Hydroisoquinolones, Diquinanes and Application to a Synthesis of (+)-Coronafacic Acid

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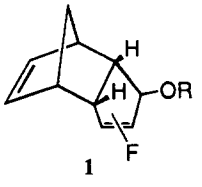
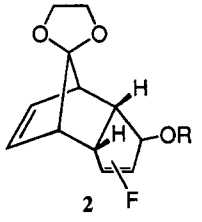
Abstract: A 5,10-dioxygenated-tricyclo[5.2.1.$0^{2,6}$]decane derivative **6** has yielded to efficient enzymatic resolution to provide a range of chiral building blocks, whose absolute configuration has been determined through a total synthesis of naturally occuring (+)-coronafacic acid.

Key Words: Enzymes; Enantiomeric purity; Indanes/Hydrindanes

Readily available monooxygenated *endo*-dicyclopentadienes like **1** have for long served as versatile building-blocks in the synthesis of diverse natural products. Extensive efforts from the groups of Zwanenburg[1a] and Ogasawara,[1b,c] on the enzymatic kinetic resolution of **1**, during the past decade, have substantially enhanced their utility as chiral synthons. The main strategic consideration in the use of **1** has been the installation of the requisite functionalization pattern on the *endo*-disposed five membered ring in a stereocontrolled manner and its retrieval through a retro-Diels-Alder reaction; a process in which half the carbon content and two carbocyclic rings of **1** are inevitably lost. On the other hand, **1** can also be recognized as a repository of six-five and five-five fused carbocyclic rings (bold portions in **3** and **4**) which can be extracted only when additional functionalization is present on the bridge carbon as in **2**. In this context, we have recently described the synthesis[2] of several hydrindane derivatives from appropriately substituted **2**, retaining its carbon and carbocyclic content. To amplify the potential use of the dioxygenated *endo*-dicyclopentadiene system **2**, we have attempted enzymatic resolution and report here preparatively useful access to enantiopure *cis*-hydrindanes, *cis*-hydroisoquinolones and diquinanes. Also described is an application of the chiral derivatives derived from **2** towards a synthesis of natural (+)-coronafacic acid.[2a]



1



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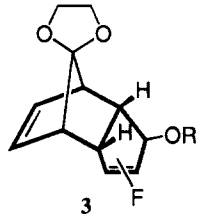

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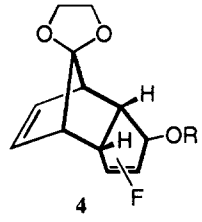

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After several attempts, it was found that fairly clear-cut kinetic acylation of *endo*-allylic alcohol **6**, readily available from enone **5**[3] on reduction, could be effected with vinyl acetate in an organic

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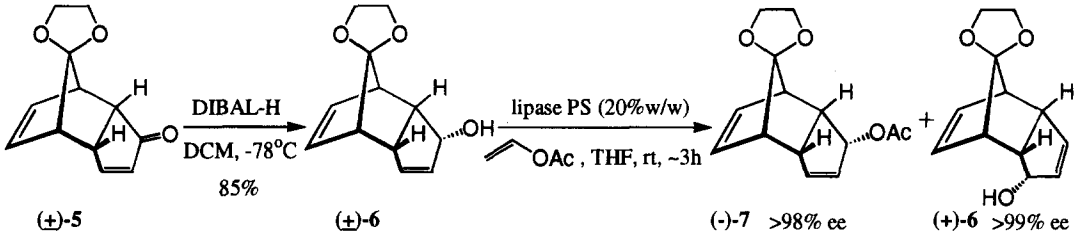
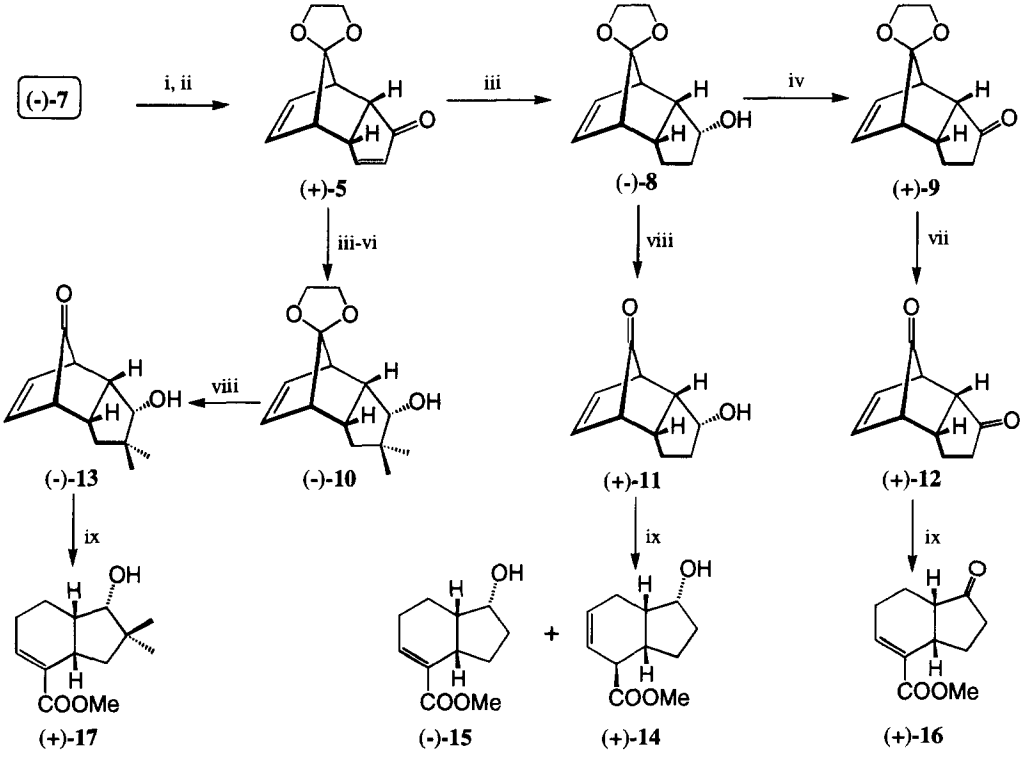
medium and lipase PS-on-celite (Amano) to furnish the acetate (-)-**7** (>98% ee, 44% yield) and alcohol (+)-**6** (>99% ee, 46% yield), Scheme 1.[4,5,6] Interestingly, only (±)-**6** was responsive to efficient enzymatic resolution; its other derivatives were either refractory or gave unproductive ee's. Thus, either (+)-**6** or (-)-**7** were deployed for further elaboration.



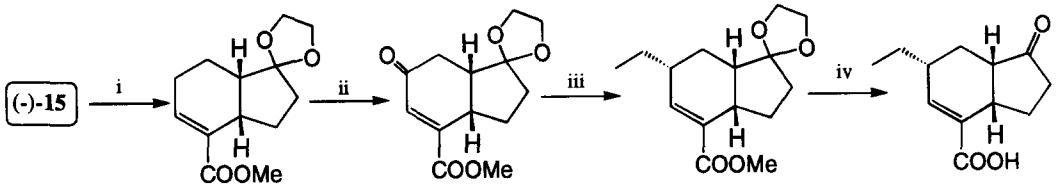
Scheme 1

For enantiopure hydrindane preparation, allylic acetate (-)-**7** was elaborated to 10-oxo-tricyclodecane derivatives (+)-**11**, (+)-**12** and (-)-**13** *via* the intermediacy of acetals **8-10**, employing routine functional group transformations, Scheme 2. In chiral ketones **11-13**, we now effected base mediated Haller-Bauer cleavage, as previously described[2a] for racemic compounds, to furnish hydrindanes (+)-**14** & (-)-**15**, (+)-**16** and (+)-**17**, respectively, in preparatively useful yields.[7] While



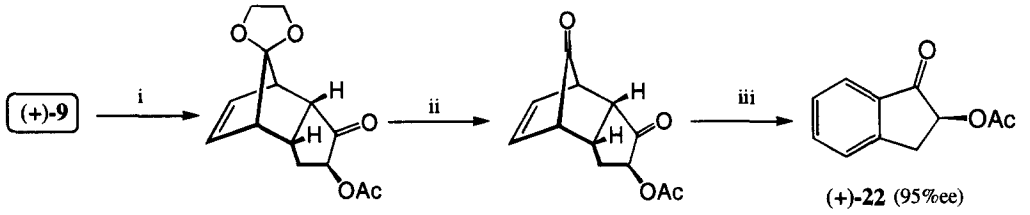
Scheme 2: i, K_2CO_3, MeOH, 100%; ii, TPAP, NMMO, 90%, iii, $NaBH_4$, EtOH, 100%; iv, PCC, DCM, 72%; v, $K^+ {}^-OBu^t$, MeI, ^tBuOH, 90%; vi, $NaBH_4$, EtOH, 100%; vii, 50%H_2SO_4, 80%; viii, Amberlyst, 90%; ix, 30- 50% aq. NaOH, benzene, Δ, then CH_2N_2, ether, 65-70%

the availability of the chiral hydrindanes was a satisfying outcome, it was essential at this stage to secure the absolute configuration of these compounds. Towards this end, (-)-**16** was elaborated to (+)-coronafacic acid **21**, $[\alpha]_D$ +105° , lit[7] $[\alpha]_D$ +109°, a natural product of known absolute stereochemistry,[8] through the intermediacy of **18-20** as outlined in Scheme 3. As an additional example of utility of these chiral tricyclodecanes in hydrindane synthesis, we have prepared 2*S*-acetoxy-1-indanone (+)-**22**,[9a] an important intermediate in the synthesis of *cis*-1-amino-2-indanols of current interest,[9b] from (+)-9 as shown in Scheme 4.



(+)-18 (+)-19 (+)-20 (+)-21

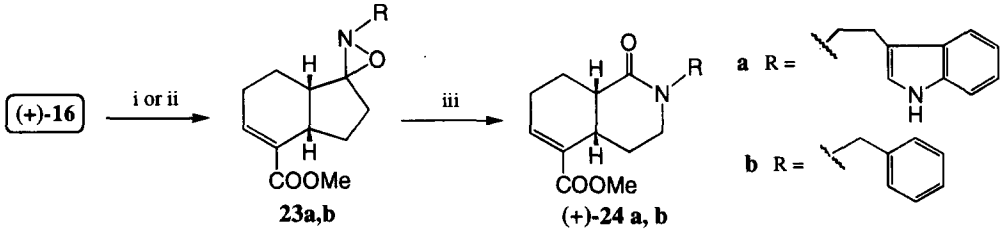
Scheme 3: i,(a) PCC, 70%; (b) ethylene glycol, PTSA, benzene, Δ, 95%; ii, PDC, t-BuOOH, 61%; iii, (a) $EtPPh_3Br$, n-BuLi, 60%; (b) H_2, Pd/C(10%), 86%; iv, 25% aq. HCl, Δ, 70%.



(+)-**22** (95%ee)

Scheme 4: i, $Pb(OAc)_4$, Δ, 80%; ii, 50% H_2SO_4, 85%; iii, ~160°C, neat, 55%.

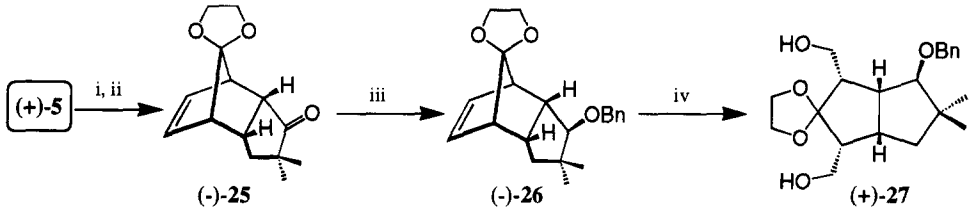
We sought to demonstrate further that the chiral hydrindanes, in turn are efficacious precursors of hydroisoquinolones of synthetic interest as shown in Scheme 5. Thus, (+)-**16** has been elaborated to **24a-b**, potential intermediates for the synthesis of alkaloids like reserpine and yohimbine, through the photorearrangement[10] of corresponding oxa-aziridines **23a-b**. It is to be noted that chiral hydroisoquinolones are not readily accessible and the present route constitutes a useful entry to these compounds.



23a,b (+)-**24 a, b**

Scheme 5: i, (a)Tryptamine, molecular sieves, ether, reflux; (b) m-CPBA, -78°C, 66%; ii, a) benzylamine, toluene, reflux, 50%; (b) m-CPBA, -78°C; iii, hν, ~60%.

Lastly, we report a synthesis of the highly functionalized chiral diquinane (+)-**27** from enone (+)-**5** involving dihydroxylation and periodate cleavage followed by reduction as the key steps and **25** & **26** serving as advanced intermediates. Since, diquinane **27** has been previously converted[11] to the triquinane natural product coriolin, our preparation of (+)-**27** can be regarded as a formal synthesis of (+)-coriolin.[12]



(-)-**25** (-)-**26** (+)-**27**

Scheme 6: i, (a) $NaBH_4$, EtOH, 100%; (b) PCC, 72%, ii, $K^+ {}^-OBu^t$, MeI, ^tBuOH, 90%; iii, (a) Li/NH_3, 70%; (b) NaH, BnBr, 90%; iv, (a) OsO_4, NMMO; (b) $NaIO_4$; (c) $NaBH_4$, MeOH, ~50%(for three steps).

In short, we have reported ready access to enantiopure 5,10-dioxygenated tricyclo[5.2.1.$0^{2,6}$] decane system through enzymatic resolution, established their absolute configuration and shown some of their potential utility in chiral synthesis through selected examples.

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[4] *Procedure for the enzymatic resolution of* (±)-**6**: A mixture of (±)-**6** (2 g, 9.7mmol) and vinyl acetate(3ml, 30mmol) in THF (15ml) was stirred with the enzyme 'lipase-PS-on-celite' (~400mg, 20% w/w) supplied by Amano, at room temperature for 3- 4 hours. The reaction mixture was filtered through a celite pad and the filtrate and the washings (dichloromethane) were evaporated under reduced pressure. The residue was chromatographed on silica gel to furnish allylic acetate (-)-**7**(1.06g, 44%), $[\alpha]_D$ - 55.7° (*c*, 1.4, $CHCl_3$) and alcohol (+)-**6** (0.94g, 46%) which was recrystallized from ether, m.p. 133-135 °C, $[\alpha]_D$ + 139.7° (*c*, 1. 7, $CHCl_3$). Enantiomeric purities were determined by NMR using chiral shift reagents and confirmed through comparison with literature values.

[5] There is one literature report on the preparation of chiral 5,10-dioxo-tricyclo[5.2.1.$0^{2,6}$]decane derivatives, obtained through classical resolution methods, for chiro-optical study of caged systems, Nakazaki M, Naemura K. J.Org.Chem.1977;42:2985.

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