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Catalytic Enantioselective Alkylative Dearomatization−Annulation: Total Synthesis and Absolute Configuration Assignment of Hyperibone K

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Abstract: The asymmetric total synthesis of the polyprenylated acylphloroglucinol hyperibone K has been achieved using an enantioselective alkylative dearomatization−annulation process. NMR and computational studies were employed to probe the mode of action of a chiral phase-transfer (ion pair) catalyst.

The polyprenylated acylphloroglucinols (PPAPs) are a unique natural product class bearing the highly substituted and oxygenated bicyclo[3.3.1]nonane-1,3,5-trione framework (Figure 1). Clusianone (**1**) and its C7 epimer **2**, isolated from the floral resins of the *Clusia* species, have been shown to have cancer chemopreventive activity[1] as well as inhibit HIV infection.[2] Hyperibone K (**3**)[3] and its structural isomer plukenetione A (**4**)[4] (absolute stereochemistries unassigned) possess highly functionalized and unusual adamantane cores. In light of their challenging structures and promising biological activities, the PPAP family has garnered significant interest. Recently, asymmetric syntheses of (+)-clusianone (**1**)[5] and (−)-hyperforin (**3**)[6] were reported. In a previous study,[7] we reported the synthesis of (±)-clusianone (**1**) employing a tandem alkylative dearomatization−annulation process. In this Communication, we report development of an enantioselective dearomatization−annulation protocol employing chiral phase-transfer (ion pair) catalysis and its application to the enantioselective synthesis of hyperibone K.

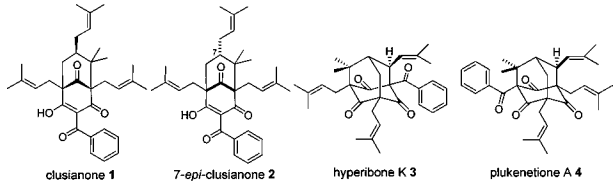
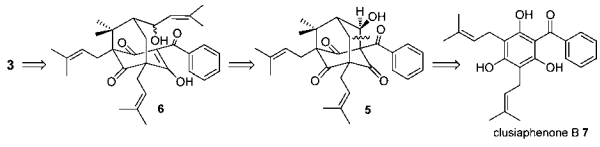


Figure 1. Polyisoprenylated acylphloroglucinol natural products.

Scheme 1. Retrosynthetic Analysis for Hyperibone K



Our approach to hyperibone K (Figure 1, **3**) leverages a concise access to adamantane **5**[7] (Scheme 1). We envisioned that **3** may be derived from allylic alcohol **6** by Lewis acid-promoted intramolecular cation cyclization.[8] Allylic alcohol **6** may be derived from base-promoted retro-aldol/vinyl metal addition[9] of adamantane **5**, the latter which may be derived from alkylative dearomatization of clusiaphenone B (**7**).

Enantioselective approaches to clusianone, hyperibone K, and other PPAPs required development of an asymmetric alkylative dearomatization−alkylation process. A number of enantioselective dearomatization processes have been reported, chiefly involving oxidation chemistry,[10] with more limited studies reported involving alkylative dearomatization.[11] Our approach was inspired by a recent report from O'Donnell and co-workers[12] involving tandem conjugate addition−elimination using a chiral phase-transfer catalyst[13] derived from *Cinchona* alkaloids. We focused our initial studies on enantioselective dearomatization/alkylation of **7** with α-acetoxy enal **9**.[7] We first evaluated a number of chiral catalysts (**8a**−**g**, Figure 2) which were prepared from readily available *Cinchona* alkaloids. In initial experiments, we found that the desired dearomatization−annulation process using *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**8a**,[14] Figure 2) ($CsOH\cdot H_2O$, 4 Å MS, CH_2Cl_2, −50 °C) proceeded smoothly to afford adamantane **5** in moderate yield (68%) and ee (75%) (Table 1, entry 1).[15] However, a stoichiometric amount of catalyst **8a** was required to promote the reaction at −50 °C.

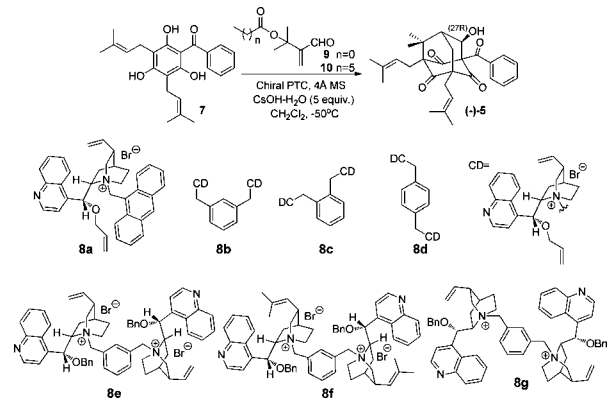


Figure 2. Dearomatization−alkylation using *Cinchona* alkaloid-derived catalysts.

Table 1. Enantioselective Dearomatization of Clusiaphenone B Using Various Phase Transfer Catalysts

Entry	Aldehyde (1.05 equiv)	catalyst (25 mol %)	time (h)	yield (%)	ee (%)
1	**9**	**8a** (1 equiv)	15	68	75 (27*R*)
2	**9**	**8b**	22	41	68 (27*R*)
3	**9**	**8c**	22	22	11 (27*R*)
4	**9**	**8d**	22	∼10	20 (27*R*)
5	**9**	**8e**	22	48	84 (27*R*)
6	**10**	**8b**	10	65	76 (27*R*)
7	**10**	**8e**	10	61	86 (27*R*)
8	**10**	**8f**	10	71	90 (27*R*)
9	**10**	**8g**	10	53	−60 (27*S*)

Recently, dimeric *Cinchona* alkaloid-derived phase-transfer catalysts have been reported,[16] which show very high reactivity and enantioselectivity in transformations including asymmetric

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alkylations[16a,d] and nucleophilic epoxidation.[16c] Accordingly, we first evaluated several reported dimeric catalysts (**8b**−**d**, Figure 2). Interestingly, we found that reactions catalyzed by the *meta*-substituted dimer **8b** (entry 2) afforded **5** in promising enantiomeric excess (68% ee) at a catalyst loading of 25 mol %. Catalysts with *ortho*- and *para*-substitution (**8c** and **8d**) showed poor enantioselectivity (11% ee and 20% ee). Through extensive structural modifications of the *meta*-dimeric catalyst, we identified the benzyl ether dimer **8e** which afforded **5** in moderate yield and good enantiomeric excess (48% yield, 84% ee).

We also evaluated heptanoate aldehyde **10** which displayed better reactivity having improved yields and shorter reaction times (Table 1, entries 6−9). Further modification of catalyst **8e** by replacing the vinyl group with a 2-methylpropenyl moiety (catalyst **8f**, entry 8) led to improvement of enantioselectivity (90% ee). Use of (+)-cinchonine-derived catalyst **8g** afforded the opposite enantiomeric product (27*S*), albeit with lower enantioselectivity (−60% ee). We were able to unambiguously determine the absolute configuration of adamantane (−)-**5** by single crystal X-ray analysis after conversion to *p*-bromobenzoate ester **11** (Figure 3).[15,17]

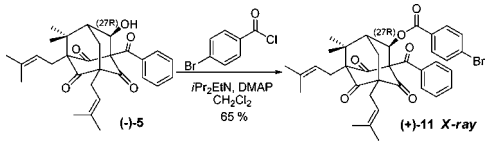
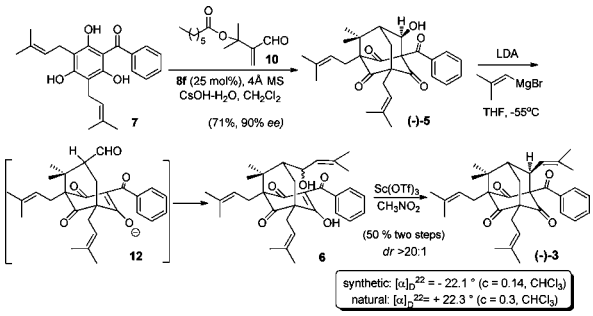


Figure 3. Determination of the absolute configuration of **5**.

Scheme 2. Total Synthesis of (−)-Hyperibone K



Our synthetic approach to hyperibone K (**3**) features a retro-aldol/addition process and is shown in Scheme 2. Dearomatization−annulation of **7** and aldehyde **10** proceeded smoothly to produce (−)-**5** (71%, 90% ee). Treatment of **5** with LDA, followed by addition of 2-methyl-1-propenyl magnesium bromide,[18] afforded allylic alcohol **6** which was produced from the retro-aldol intermediate **12** followed by addition of 2-methyl-propenyl magnesium bromide. Intramolecular cation cyclization of **6** catalyzed by $Sc(OTf)_3$[8] successfully afforded (−)-**3** in moderate yield (50% yield, two steps), thus establishing the absolute configuration of natural (+)-**3**. The high (>20:1) diastereoselectivity observed in the cyclization may be explained by analysis of cationic intermediate **13** which indicates a likely preference for conformation **13a** wherein the allylic cation is situated away from the *gem*-dimethyl moiety (Figure 4).

Although we developed an efficient catalyst system for enantioselective dearomatization−annulation, the mechanism and mode of action for the phase-transfer (ion pair) catalyst remained unsolved. To further understand the catalyst mode of action, we considered a two-stage approach which would utilize both experimental and computational information. Stage 1 involved understanding the identity of the reactive substrate and relevant conformation(s) for the catalyst. Stage 2 involved elucidation of the substrate and catalyst complex leading to the observed enantiomer (−)-**5**.

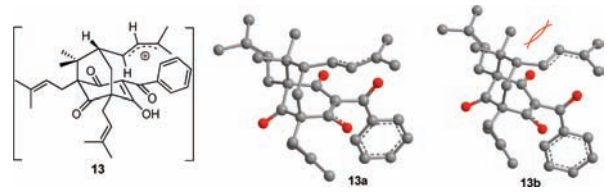


Figure 4. Allylic cation intermediate **13**.

Accordingly, initial ^{1}H NMR studies were conducted which indicated that, under standard reaction conditions (both achiral and chiral phase transfer catalysts), 80−90% of clusiaphenone B **7** exists in a dearomatized enolate form (*cf.* **14**−**17**, Figure 5).[15,19] Accordingly, we propose that the dearomatized enolate is likely the reactive species interacting with the catalyst.

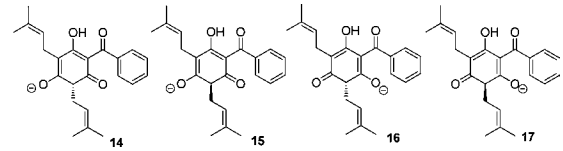


Figure 5. Dearomatized acylphloroglucinols **14**−**17**.

We next turned our attention to elucidating the catalyst conformation. ^{1}H and ^{13}C NMR analysis of dimeric catalyst **8e** indicated that the catalyst adopts a *C*2 symmetrical conformation which is in agreement with a previously reported crystal structure of a related dimeric *Cinchona* alkaloid-derived catalyst.[16c] We utilized NOESY experiments in conjunction with conformational analysis (mixed Monte Carlo Multiple Minimum (MCMM)/Low-Mode Conformational Search (LMCS)) to determine likely conformations of catalyst **8e** in solution. By surveying the generated low energy conformations corresponding to key NOE interactions, we identified a single conformation (Figure 6) which was further optimized using DFT (B3LYP-63-1g). We also compared NOESY data of **8e** both alone and with substrate **7** allowing us to ascertain that the catalyst conformation did not shift significantly upon substrate complexation.[15]

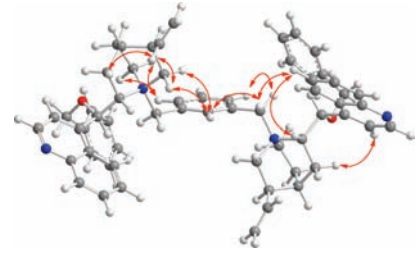


Figure 6. Optimized conformation of catalyst **8e** with key NOEs.

Stage 2 relied on use of computational molecular docking to generate binding poses of the catalyst substrate complex. Literature reports have indicated the possibility of this approach highlighted by an example from Deslongchamps and co-workers who have utilized reverse docking to explore the configurational space of a flexible organocatalyst around a rigid catalyst-free transition state.[20] We utilized CDOCKER (a CHARMM-based docking program) to systematically pose the flexible substrate (acylphloroglucinol) within a static catalytic site and conduct low-level energy calculations for each pose. We also combined these studies with ROESY data of the substrate catalyst complex which illuminated key intermolecular interactions.[15]

As there are several possible enolates which may be operative (cf. Figure 5), we conducted docking studies on each. Docking experiments provided over 100 poses for enolates **14**−**17** bound

to **8e** which were quickly reduced to a single pose for each enolate through a series of criteria: (1) correlation with ROESY data; (2) potential for ion-pair interactions (2−4 Å); and (3) substrate availability for Michael addition. The selected pose for each enolate was further optimized by DFT (B3LYP-63-1g).[15] Poses meeting most of these criteria for each substrate were very similar regarding placement of the dearomatized enolate in the catalyst cavity.

Utilizing a pose which meets all of the criteria above, we developed a working model for the phase-transfer (ion pair) catalyst-mediated dearomatization−annulation with **8e** and enolate **15** (Figure 7). The preferred binding mode appears to be one in which the *para*-enolate oxygen is placed near a quaternary nitrogen center to form a tight ion pair and the dearomatized cyclohexadienone is aligned near the top of the aromatic linker. The lower energy poses situate the substrate such that the pseudoaxial proton derived from dearomatization is oriented away from the catalyst (Figure 7a).[15] In this orientation, substrates **15** and **17** appear to have more optimal ion pairing (Figure 7a) with the more accessible ammonium center while substrates **14** and **16** are situated such that the charge bearing oxygen is paired with the less accessible ammonium center.[15] The pose illustrated in Figure 7 also satisfies the major intermolecular interactions identified by ROESY experiments (Figure 7a).[15] Furthermore, poses utilizing substrates **15** and **17** may lead to the correct stereochemical outcome ((−)-**5**) while poses with **14** and **16** would afford the opposite configuration.[15] Based on the model of catalyst **8e** and substrate **15**, it is apparent that a key binding element involves hydrophobic interaction of a substrate prenyl group in a hydrophobic cleft of the catalyst formed by the vinyl and *O*-benzyl groups (Figure 7b), both of which were shown to be critical for enantioselectivity (cf. Table 1).[17]

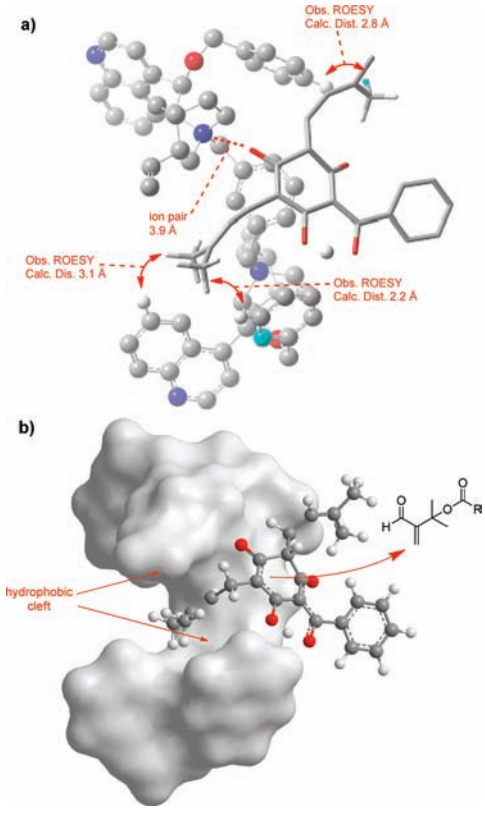


Figure 7. Proposed Binding Model of Catalyst **8e** and **15**. (a) Key interactions of **8e** and **15**. (b) 1.4 Å Connolly surface.

In summary, we have developed an enantioselective alkylative dearomatization−annulation process using dimeric chiral phase-transfer (ion pair) catalysts. The total synthesis and absolute configuration assignment of hyperibone K have been achieved by application of the asymmetric dearomatization process. NMR and computational studies were employed to illuminate the mode of action for the phase-transfer (ion pair) catalyst. Further studies utilizing molecular docking for a mechanistic understanding of phase-transfer catalysis are ongoing and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Interestingly, reaction of the *bis*-allyl variant of clusiaphenone B with **9** and catalyst **8e** (25 mol%) (−35°C, 42 h) afforded the corresponding adamantane alcohol in 11% yield. Olefin cross-metathesis afforded (−)-**5** in 39% ee which underscores the importance of the prenyl groups in substrate **7** for enantioselectivity.
(18) Use of 2 equiv of 2-methyl-propenyl lithium also promoted retro-aldol/addition in comparable yield.
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