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Opening Norbornadiene Homo Diels-Alder Adducts to Bicyclic Systems

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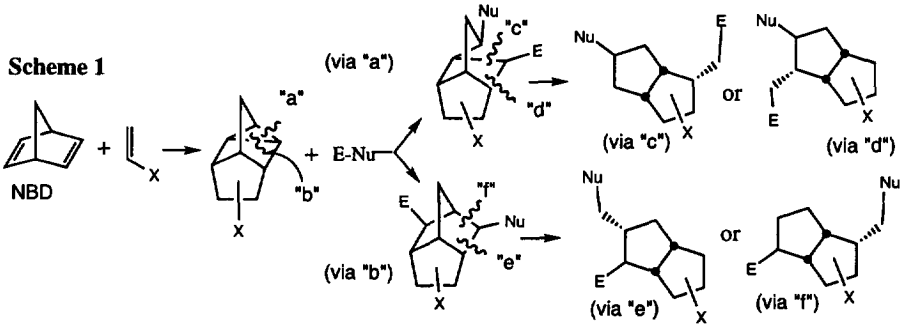
Abstract: Deltacyclenes and deltacyclanes produced from the [2+2+2] homo Diels-Alder reaction of norbornadiene are opened to the corresponding biquinanes. Similarly, opening the [4+2+2]-adducts yields the bicyclo[5.3.0]decanes.

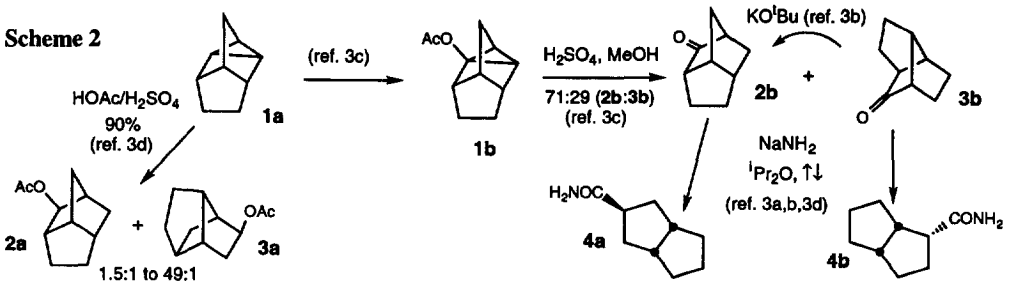
The homo Diels-Alder reactions of norbornadiene (NBD) are some of the more intriguing reactions in organic chemistry.[1] Conceptually, sequential bond cleavages of the [2+2+2]-adduct deltacyclane (or deltacyclene from cycloadditions with alkynes) leads to biquinane systems via intermediate brendanes or brexanes (Scheme 1). The potential for creating up to nine new chiral centers from achiral, appropriately substituted presursors in a single transformation with installation of desired functionality in the course of the ring-openings, as well as the successful use of chiral ligands in the transition metal catalyzed cycloaddition for achieving high levels of enantioselectivity reported by several groups,[1,2] makes this chemistry an attractive area for investigation.

Scheme 1



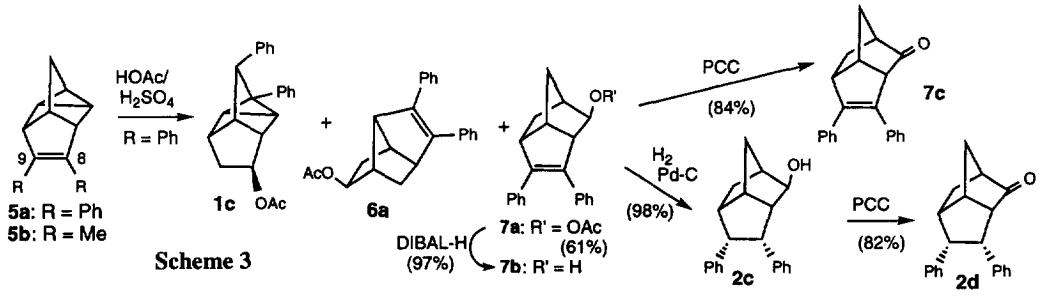
The transformation of the deltacyclane skeleton to a biquinane has previously been accomplished by Nickon, giving hope that synthetically useful amounts of biquinanes might be available following this strategy.[3] In this work, acid promoted opening of deltacyclane **1a** or acetoxydeltacyclane **1b** to the brendane or brexane systems (**2** and **3**, respectively) followed by Haller-Bauer reactions led to biquinanes **4a** and **4b** (Scheme 2). Rigby and Lee,[4] and Heumann[5] have also reported Baeyer-Villager oxidations of 2-brendanones, ultimately producing biquinanes, though the starting brendanones were not prepared from deltacyclanes. Our strategy was to assemble the deltacyclane using a transition metal promoted [2+2+2]-homo Diels-Alder reaction followed by

Scheme 2



electrophilic opening (H^+) of the cyclopropyl ring to the brendane skeleton, with subsequent Baeyer-Villager oxidation or alkoxy radical fragmentation to the biquinane, in essence combining the chemistry of Lautens, Nickon and others to access the desired bicyclic system. A similar strategy would also be applied to the [4+2+2] homo Diels-Alder adducts of NBD.[6]

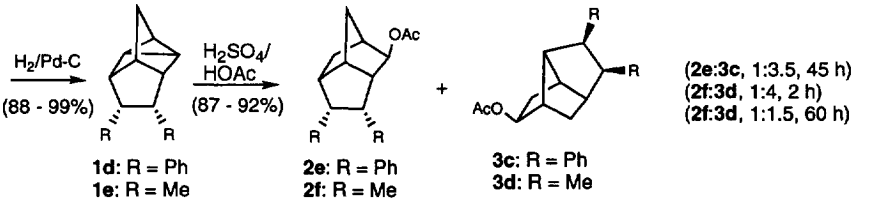
Initial studies began with the the deltacyclenes **5a/b**.[7] Adapting the precedence of Nickon,[3d] **5a** opened in H_2SO_4/HOAc (0.17 M **5a**, 0.5 g H_2SO_4/100 mL HOAc, rt) to provide a mixture of brendene **7a**, brexene **6a** and deltacyclane **1c**[8] in a combined yield of 92% (**7a**:**6a**:**1c**, 46:21:33, Scheme 3). Increasing reaction time led to increased amounts of **7a** at the overall expense of **1c** with the yield of **7a** optimized at 61% after 7 days (**7a**:**6a**:**1c**, 62:21:17). In contrast, **5b** reacted initially by addition of acetic acid across the double bond followed by further chemistry to provide a complex mixture of products. Conversion of acetate **7a** to brendenol **7b** and brendenone **7c**, respectively, was routine. In addition, **7b** was smoothly hydrogenated to **2c** (98%), with ketone **2d** (82%) obtained by the subsequent oxidation.



Scheme 3

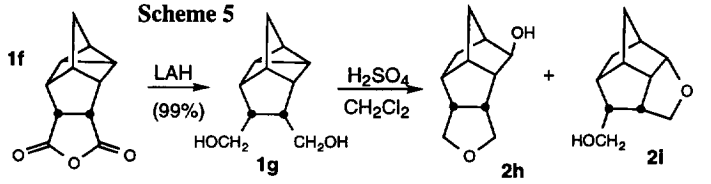
In an attempt to open the cyclopropane ring of the deltacyclane skeleton without complications arising from the intervention of the deltacyclene double bond, **5a/b** were hydrogenated to produce deltacyclanes **1d/1e** (Scheme 4). Treatment of **1d/e** under the Nickon conditions produced a mixture of brendane **2e/f** and brexane **3c/d** acetates with the brexanes predominating in combined yields ranging of 87 - 92%. The product ratioes were sensitive to reaction times. While the diphenyl derivatives **2e/3c** were separable by SiO_2 chromatography, **2f/3d** were not, nor were the corresponding alcohols produced by DIBAL-H reduction.[9] The dominance of the brexyl acetates in the acid promoted opening of 8,9-disubstituted deltacyclanes **1d/1e** contrasts with the unsubstituted deltacyclane which favored the brendane system (Scheme 2), and presumably reflects the more hindered endo orientation of the "R" substituents in the brendanes **2e/2f**.

Scheme 4



Since the brendane system is the desired intermediate to the biquinanes, we examined the possibility of intramolecular trapping the intermediate carbocation produced by acid opening of the deltacyclane, with a suitably position nucleophile that would hold the brendyl form, as in **1g** most easily prepared from the maleic anhydride adduct **1f**[10] (Scheme 5). Treatment of **1g** with H_2SO_4 in CH_2Cl_2 produced the brendanes **2h** and **2i** with no brexanes detected; the ratio **2h**:**2i** depended upon the amount of H_2SO_4 employed and the time of reaction. With only 20 mol% H_2SO_4 and 7 h reaction time, **2h** predominated 78:22 (99% combined yield). In contrast, treatment of **1g** with 2 eq. H_2SO_4 for only 10 min produced predominantly **2i** (81%) with only a small amount of **2h** (8%). Surprisingly, neither **2h** nor **2i** equilibrated when resubjected to the acidic conditions.

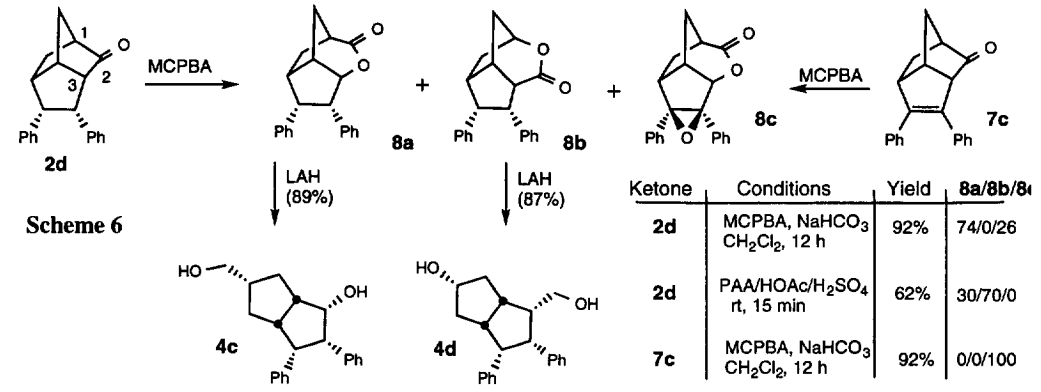
Scheme 5



Conditions	Yield (NMR)	2h:2i
H_2SO_4 (20 mol%), rt, 7 h	99%	78:22
H_2SO_4 (2 eq), rt, 10 min	89%	8:92

Baeyer-Villager oxidation of brendanone **2d** produced a mixture of regioisomeric lactones **8a** and **8b**, the ratio of which depended significantly upon the conditions of the oxidation[11] (Scheme 6). Optimal yield of the C2/C3 bond migration was achieved under basic conditions (MCPBA, $NaHCO_3$) producing lactone **8a** and epoxide **8c**. In contrast, use of acidic conditions gave lower regioselectivity producing **8a** and **8b** with the latter predominating 7:3. Following separation, reduction (LAH) of the lactones produced the corresponding diols **4c** (89%) and **4d** (87%), thereby completing the route to the biquinanes. Application of the basic Baeyer-Villager conditions to brendenone **7c** gave solely lactone epoxide **8c** (92%).

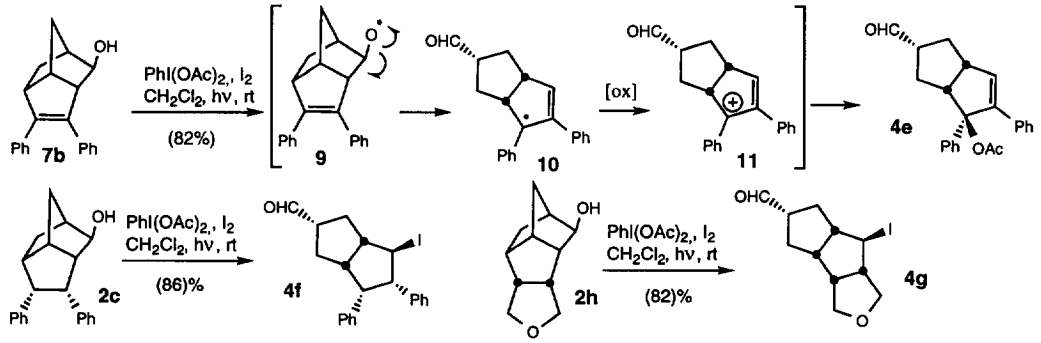
Scheme 6



Ketone	Conditions	Yield	8a/8b/8c
2d	MCPBA, $NaHCO_3$ CH_2Cl_2, 12 h	92%	74/0/26
2d	PAA/HOAc/H_2SO_4 rt, 15 min	62%	30/70/0
7c	MCPBA, $NaHCO_3$ CH_2Cl_2, 12 h	92%	0/0/100

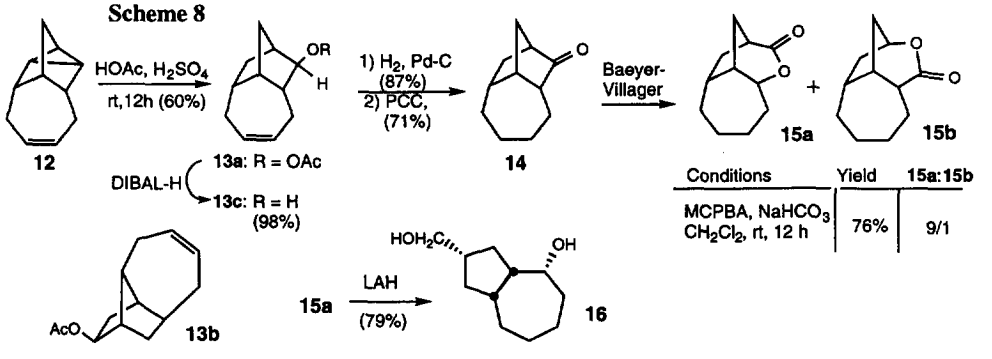
Suarez cleavage[12] to open the brendane skeleton was also examined. Photolysis of **7b** in the presence of $PhI(OAc)_2$ and I_2 gave **4e** as the major product (Scheme 7). This product presumably results from alkoxide radical **9** fragmentation to allylic radical **10**. Further oxidation to benzylic carbocation **11** which is subsequently captured by acetate gives **4e**. Under the same conditions saturated alcohols **2c** and **2h** gave iodides **4f** (86%) and **4g** (57%), respectively. In both reactions, minor amounts of the presumed iodide epimers were detected in the crude NMR spectra.

Scheme 7



Adaptation of these ring-opening procedures to the [4+2+2]-adduct of norbornadiene with butadiene was briefly investigated. Adduct **12**[6d] underwent cyclopropane opening in H_2SO_4/HOAc to produce a mixture of **13a** and **13b** (69:31, **13a**:**13b**) with 60% isolated yield of **13a** (Scheme 8). Alcohol **13c** was obtained from **13a** (DIBAL-H, 98%) which was subsequently hydrogenated, then oxidized to ketone **14**. Suarez cleavage of **13c** produced a complex mixture of aldehydes, but Baeyer-Villager oxidation of **14** produced lactones **15a** and **15b**, the ratio of which varied with the conditions, but yielding **15a** as the main product under acidic and basic conditions. Opening **15a** to the bicyclo[5.3.0]decane **16** with LAH (79%) completed the formation of the desired bicycle.

Scheme 8



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