Communications

Preparation of Enantiomerically Pure 1,6-Methano[10]annulene Derivatives

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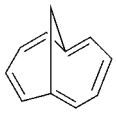
Received June 23, 1997

Since the original preparation of the parent 1,6-methano[10]annulene by Vogel and Roth,[1] annulene derivatives have been the subject of numerous investigations dealing with both theoretical[2] and, more recently, biological[3] issues stemming from the novel properties and structures of these interesting species. In conjunction with these studies, several useful synthetic approaches into a variety of methanoannulene systems have been developed.[4] As the demand grows for access to more substitutionally elaborate annulenes to support these studies, methods for preparing derivatives in enantiomerically enriched form become increasingly significant.



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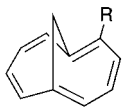

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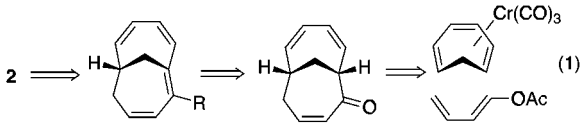
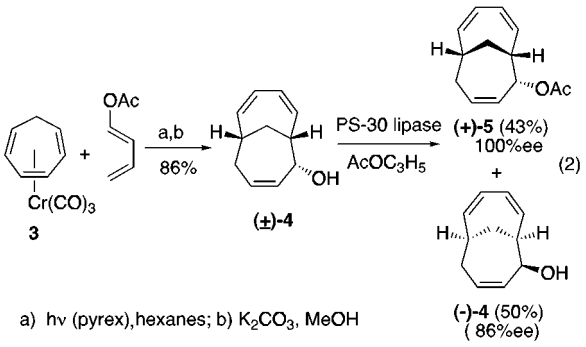
1,6-Methano[10]annulene (**1**) itself possesses C_{2v} symmetry but becomes chiral (planar chirality) with the introduction of a non-hydrogen substituent at any position around the perimeter of the π-framework (i.e., compound **2**).[5] Furthermore, empirical evidence suggests that the configurational stability of the bridge is sufficiently high to permit isolation of enantiomeric forms at ambient temperatures. For example, the inversion barrier of a closely related oxido-bridged [10]annulene species has been estimated to be at least 42 kcal/mol^{-1}.[6] To date, however, relatively few chiral, nonracemic annulenes have been prepared and characterized. In most instances classical resolution techniques[7] or chiral chromatographic separation of racemic mixtures have been employed to isolate enantiomerically enriched annulenes.[8]



We now disclose a new method for the construction of planar chiral 1,6-methano[10]annulenes in enantiomerically enriched form. The strategy employed in these studies features an enzymatic resolution of substituted bicyclo[4.4.1]undecatrienes, which are conveniently available via chromium(0)-promoted [$6\pi + 4\pi$] cycloaddition. (eq 1).[9] An advantage of this approach is the capability of delivering chiral, nonracemic annulenes that may not be amenable to traditional resolution.



The preparative sequence begins with an efficient photocycloaddition between complex **3** and 1-acetoxybutadiene that affords, after saponification, the known bicyclic alcohol (±)-**4**[9c] in excellent yield. It is noteworthy that metal-promoted higher-order cycloadditions are known to proceed with high diastereoselection via an *endo* reaction pathway.[9] Although auxiliary-controlled methods for asymmetric induction during the cycloaddition event itself have been established previously,[9d] enzymatic resolution was regarded as a more attractive prospect for delivering enantiomerically enriched substrates in the present context. Toward this end, exposure of the racemic alcohol **4** to Amano PS-30 lipase[10] in isopropenyl acetate under standard conditions for 68 h at room temperature afforded (+)-**5** and (−)-**4** in 43%(100%ee) and 50%(86%ee) yields, respectively. The enantiomeric purity of each compound was determined by conversion into the R-α-methoxyphenylacetate ester, and the absolute configuration of (+)-**5** was established by an X-ray structure determination of the methoxyphe-

† Author to whom inquiries regarding X-ray structure determinations should be directed.

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(4) For some representative preparative methods, see: (a) Barrett, D. G.; Liang, G.-B.; McQuade, D. T.; Desper, J. M.; Schladetzky, K. D.; Gellman, S. H. *J. Am. Chem. Soc.* **1994**, *116*, 10525. (b) Barrett, D. G.; Liang, G.-B.; Gellman, S. H. *Ibid.* **1992**, *114*, 6915. (c) Paquette, L. A.; Heyd, W. E.; Thompson, G. L. *Ibid.* **1974**, *96*, 3177. (d) Vogel, E.; Schröck, W.; Böll, W. A. *Angew. Chem., Intl. Ed. Engl.* **1966**, *5*, 732.

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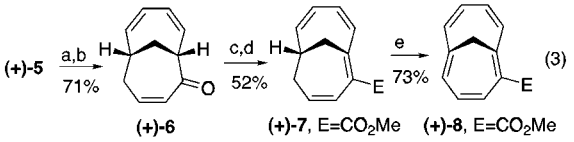
S0022-3263(97)01137-7 CCC: $14.00

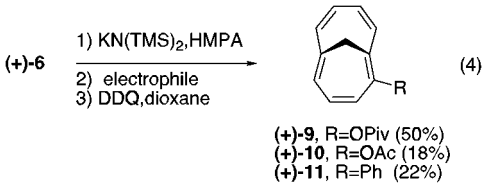
nylacetate derivative of the corresponding alcohol.[11] This is the first example of an enzyme-mediated resolution of the bicyclo[4.4.1]undecane ring system.

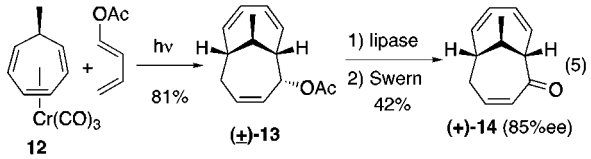


a) K_2CO_3 , MeOH; b) $(COCl)_2$, DMSO, TEA.; c) $KN(TMS)_2$, HMPA/THF, -78°; $PhN(OTf)_2$, THF; d) $Pd(OAc)_2$, PPh_3,TEA; e)DDQ, dioxane, reflux.

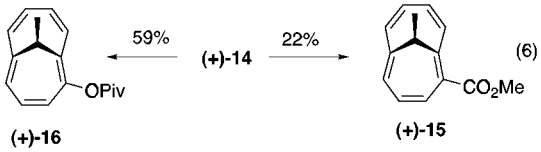
Swern oxidation of the alcohol derived from (+)-**5** afforded enone (+)-**6**,[12] which was envisioned to be the key building block from which a range of substituted annulenes could be assembled. No evidence of epimerization at the bridgehead position was noted during the oxidation step. It is noteworthy that the epimer of (+)-**6** would possess a so-called inside, outside-interbridgehead stereochemical relationship, which is well-known to be a relatively high-energy spatial arrangement in the bicyclo[4.4.1]undecane system.[13] The utility of enone (+)-**6** in 1,6-methano[10]annulene synthesis is crucially dependent on the ability to efficiently generate and trap the corresponding bridgehead enolate within the bicyclic framework. At the outset, this objective seemed attainable since it had been previously demonstrated that enolates of this type in the bicyclo[4.4.1]undecane ring system are well-behaved and react efficiently with numerous electrophiles.[14] Thus, treatment of (+)-**6** with $KN(TMS)_2$ followed by quenching with *N*-phenyltriflamide afforded the requisite vinyl triflate. This species was regarded as a versatile point of departure for effecting various carbon−carbon bond constructions around the annulene perimeter, and the preparation of 2-substituted species became the initial focus of the current study. In the event, the somewhat labile triflate was immediately exposed to the Ortar Pd(0)-mediated carbomethoxylation protocol[15] to afford tetraene ester (+)-**7**[12] in good yield. Routine dehydrogenation[4c] with DDQ in refluxing dioxane gave 1,6-methano[10]annulene (+)-**8**[12] $[\alpha]^{20}_D = +269$, lit.[7] $= +266$), which was identical in all regards to the known enantiomerically pure compound obtained previously by Schlögl and co-workers using classical resolution techniques.[7] It is noteworthy that the entire sequence from (+)-**5** to (+)-**8** occurred with no apparent erosion of enantiomeric purity.

The same sequence of steps can provide access to a number of other chiral, 2-substituted 1,6-methano[10]-annulenes as outlined in (eq 4). For example, trapping of the bridgehead enolate with pivaloyl chloride or acetyl chloride afforded the corresponding esters (+)-**9**[12] and (+)-**10**,[12] respectively, and Suzuki arylation[16] of the triflate derivative ($PhB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4) afforded (+)-**11**[12] in serviceable yield.





More highly substituted 1,6-methano[10]annulenes are also readily available via this route. In a typical case, cycloaddition of complex **12**,[17] which can be prepared in diastereomerically pure form, afforded the racemic adduct (±)-**13**[12] in excellent yield. This material was again subjected to enzymatic resolution using PS-30 lipase; however, in this instance, the hydrolysis direction proved to be superior for delivering enantiomerically enriched product. Swern oxidation then afforded enone (+)-**14**[12] (85% ee), which was easily transformed into several chiral annulenes via manipulation of the bridgehead enolate in a fashion completely analogous to the examples described previously (eq 6).



In summary, the combination of metal-promoted [6π + 4π] cycloaddition and enzymatic resolution of the resultant bicyclo[4.4.1]undecatriene products provides efficient and general access to a variety of chiral, nonracemic racemic 1,6-methano[10]annulene derivatives.

Acknowledgment. The authors thank the National Institutes of Health (GM-30771) for their generous support of this research.

Supporting Information Available: Typical procedures for enzymatic resolution and 1,6-methano[10]annulene synthesis. Listings of characterization data for (+)-**5**, (+)-**6**, (+)-**7**−(+)-**11**, (+)-**15**, and (+)-**16**. Crystallographic information for the (*R*)-α-methoxyphenylacetate derivative of (+)-**4** (tables of atomic coordinates, thermal parameters, bond lengths, bond angles, and torsion angles) (14 pages).

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(11) The enzyme resolution was performed in the synthetic direction in this case since both the chemical yield and enantiomeric purity of the desired product were higher than obtained by hydrolysis of the acetate derivative.

(12) This compound exhibited spectral (^{1}H NMR, ^{13}C NMR, IR) and analytical (HRMS and/or combustion analysis) data consistent with the assigned structure.

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