Pergamon

Tetrahedron Letters, Vol. 37, No. 40, pp. 7241-7244, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01629-2

Synthesis of (1*R*)-(+)-Nopinone- and (1*S*)-(-)-Verbenone-Derived Chiral Annulated Indenes via Electrocyclic Reactions

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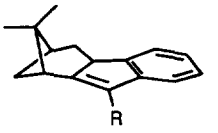
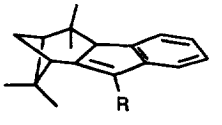
Abstract: Two new chiral annulated indene derivatives have been stereoselectively synthesized via acid-catalyzed electrocyclic reactions from naturally occurring homochiral precursors (1*R*)-(+)-nopinone and (1*S*)-(-)-verbenone.

Chiral indenes are useful ligands for transition metal complexes in asymmetric transformations.[1] While most chiral indenes are prepared as bridged bis(indenes)[2] or with a chiral substituent,[3] synthesis of chiral annulated indenes are scarce.[2a] A practical synthesis of chiral annulated indenes can be envisioned by fusing a chiral bicyclic auxiliary derived from nature's chiral pool to an indene moiety.[4] Thus, we have investigated a synthetic route involving initial formation of a chiral phenyl-substituted allylic alcohol through a Shapiro reaction,[5] and a subsequent annulation via Nazarov cyclization[6,7] to form chiral annulated indenes. We report the synthesis of indene derivatives **1** and **2**, starting from bicyclic ketones (1*R*)-(+)-nopinone and (1*S*)-(-)-verbenone, respectively. The structural rigidity of the chiral skeleton and versatility of the preparation of the substituted derivatives will provide attractive features when the compounds are used as chiral ligands for transition metal mediated asymmetric transformations.



1: R = Ph

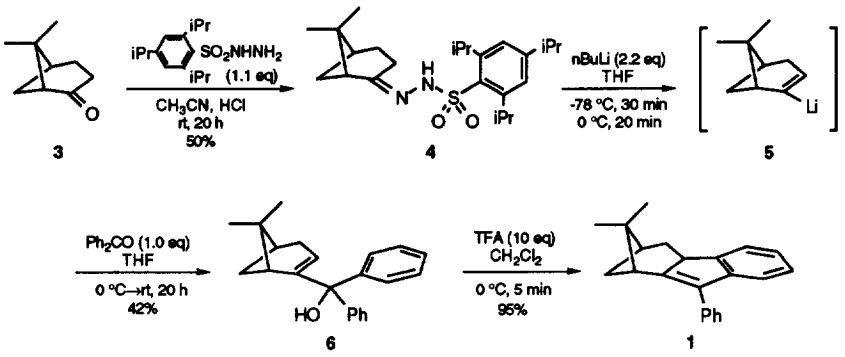


2a: R = Ph
2b: R = CH_3

The synthetic approach to chiral annulated indene **1** starts from (1*R*)-(+)-nopinone (**3**) as shown in Scheme I. In the three-step synthesis, the trisylhydrozone **4** is prepared and then is treated with nBuLi in THF to provide vinyllithium **5**, which is subsequently coupled with benzophenone to form the phenyl-substituted allylic alcohol **6**. By using appropriately functionalized phenyl ketones we can potentially incorporate different substituents into the indene core of **1**. To obtain the desired annulated indene, acid-catalyzed electrocyclic reactions of allylic alcohol **6** were investigated under various conditions. For example, treatment of **6** with

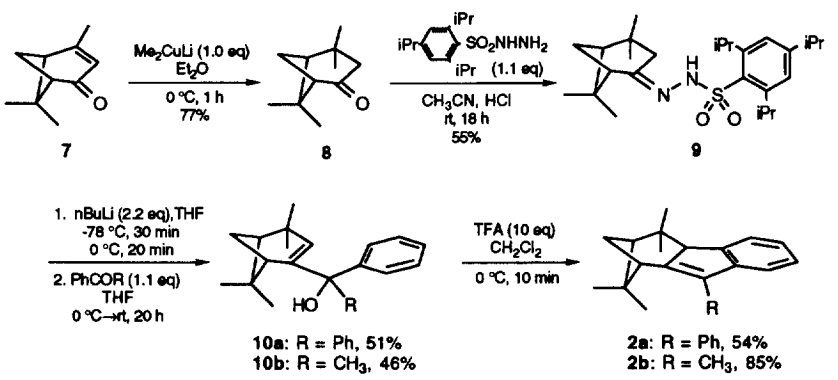
molecular sieves in benzene at room temperature gave a mixture of an elimination product, an unknown product and the desired cyclization product. However, we find that cyclization proceeds optimally in the presence of trifluoroacetic acid (TFA) to afford the desired chiral indene **1**.[8]

Scheme I

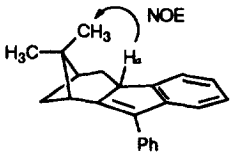


The chiral bicyclic framework was also constructed based on commercially available (1*S*)-(-)-verbenone (**7**) with a chemical modification (Scheme II). Conjugate addition of a methyl group to **7** with lithium dimethylcuprate provides the chiral ketone **8**[4j] which differs from nopinone **3** in absolute configuration and in having another pair of geminal methyl groups adjacent to the carbon to be fused on the indene subunit. The geminal methyl groups prevent the problematic elimination reaction observed in the nopinone derivative. The synthesis of verbenone-derived chiral annulated indenes **2a-b** is similar to that of **1**. Thus, treatment of **9** with nBuLi in THF followed by reaction with the appropriate phenyl ketone provides the allylic alcohols **10a-b**. The allylic alcohol **10b** is observed as a 1:1 mixture of two diastereomers which is separated by flash chromatography. The alcohols **10a-b** are readily cyclized in the presence of TFA to form the chiral indenes **2a-b**.[9]

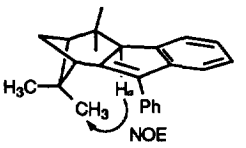
Scheme II



It is interesting to note that only one of two possible diastereomers of the fused indene products **1** and **2a-b** is observed under the reaction conditions as indicated by ^{1}H and ^{13}C NMR spectral data. The stereochemistry of the hydrogen atom at the ring fusion, for both molecules **1** and **2a**, is assigned by NOE difference experiments. Enhancement at the protons of one of the bridgehead geminal methyl groups (**1**, CH_3 δ1.27, 3.4% NOE; **2a**, CH_3 δ0.82, 4.4% NOE) upon irradiation of the proton at ring fusion (**1**, H*a* δ4.19; **2a**, H*a* δ4.16) indicates that the methyl group and the hydrogen atom at ring fusion are on the same face of the molecule. The common stereochemical feature of these two molecules can be explained by torquoselectivity[7] of the allowed conrotatory electrocyclization; only one of two possible pathways is observed. The observed product arises from bond formation from the less hindered side of the bicyclic framework.



1



2a

In summary, the synthesis of nopinone- and verbenone-derived chiral annulated indenes provides an efficient route to form novel and potentially useful chiral ligands. This study, to our knowledge, is the first that shows a Nazarov cationic electrocyclization involving both an aromatic ring and an allylic double bond in a rigid bicyclic structure.[7,10] The stereoselective formation of the chiral indenes is intriguing for its mechanistic aspects and synthetic generality. Extending the synthesis to other substrates, metallation of these chiral indenes, and application in asymmetric transformations are the focus of current investigations.

Acknowledgment: This work was partially supported by a grant from Amoco Chemical, Inc.

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8. Intermediates **4** and **6** are characterized by ^{1}H NMR, ^{13}C NMR and HRMS. Spectral data for **1**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.46-7.16 (m, 9H), 4.19 (dd, *J* = 7.6 Hz, 1H), 3.26 (t, *J* = 5.6 Hz, 1H), 2.81 (m, 1H), 2.76 (m, 1 H), 2.21 (m, 1H), 1.99 (m, 1H), 1.40 (s, 3H), 1.27 (s, 3H), 0.87 (d, *J* = 9.5 Hz, 1H); ^{13}C NMR and ^{13}C-DEPT NMR ($CDCl_3$, 50 MHz), combined, δ 156.1, 147.3, 146.0, 135.5, 132.2, 128.9, 128.4, 128.0, 127.7, 126.8, 126.0, 123.7, 121.9, 119.1, 46.6, 46.1, 42.3, 40.1, 39.2(i), 29.4(i), 28.3, 23.8; MS (EI, 70 eV) m/e(relative intensity) 105(57), 165(81), 181(38), 202(62), 217(100), 233(79), 245(96), 259(22), 286(71); HRMS m/e (M^+) 286.1722, calcd for $C_{22}H_{22}$ 286.1722.
9. Intermediates **8**, **9**, **10a-b** are characterized by ^{1}H NMR, ^{13}C NMR and HRMS. Spectral data for **2a**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.48-7.15 (m, 9H), 4.16 (s, 1H), 3.17 (t, *J* = 5.7 Hz, 1H), 2.61 (m, 1H), 1.85 (t, *J* = 5.3 Hz, 1H), 1.57 (s, 3H), 1.42 (s, 3H), 1.34 (s, 3H), 1.20 (d, *J* = 9.9 Hz, 1H), 0.82 (s, 3H); ^{13}C NMR and ^{13}C-DEPT NMR ($CDCl_3$, 50 MHz), combined, δ 154.3, 146.5, 143.9, 135.6, 132.7, 129.0, 128.4, 126.7, 125.9, 123.7, 123.3, 119.2, 56.7, 56.6, 45.7, 41.0, 37.2, 35.4(i), 31.2, 29.2, 26.0, 25.3; MS (EI, 70 eV) m/e(relative intensity) 97(100), 193(29), 215(31), 229(18), 245(39), 271(15), 314(30); HRMS m/e (M^+) 314.2041, calcd for $C_{24}H_{26}$ 314.2035. Spectral data for **2b**: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.43–7.07 (m, 4H), 3.98 (s, 1H), 3.08 (t, *J* = 5.4 Hz, 1H), 2.57 (m, 1H), 1.98 (d, *J* = 2.5 Hz, 3H), 1.80 (t, *J* = 5.4 Hz, 1H), 1.50 (s, 3H), 1.45 (s, 3H), 1.30 (s, 3H), 1.02 (d, *J* = 10.0 Hz, 1H), 0.71 (s, 3H); ^{13}C NMR and ^{13}C-DEPT NMR ($CDCl_3$, 50 MHz), combined, δ 151.5, 148.1, 144.0, 126.8, 125.8, 123.2, 122.9, 118.0, 57.0, 56.3, 45.1, 41.3, 36.9, 35.2(i), 31.3, 29.4, 25.8, 25.3, 10.0; MS (EI, 70 eV) m/e(relative intensity) 252(27), 209(28), 183(40), 97(100); HRMS m/e (M^+) 252.1873, calcd for $C_{19}H_{24}$ 252.1878.
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(*Received in USA* 17 *July* 1996; *accepted* 13 *August* 1996)