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AN ASYMMETRIC ROUTE TO FUSED CARBOCYCLIC SYSTEMS *VIA* DIELS-ALDER REACTIONS ON CHIRAL α,β-UNSATURATED BICYCLIC LACTAMS

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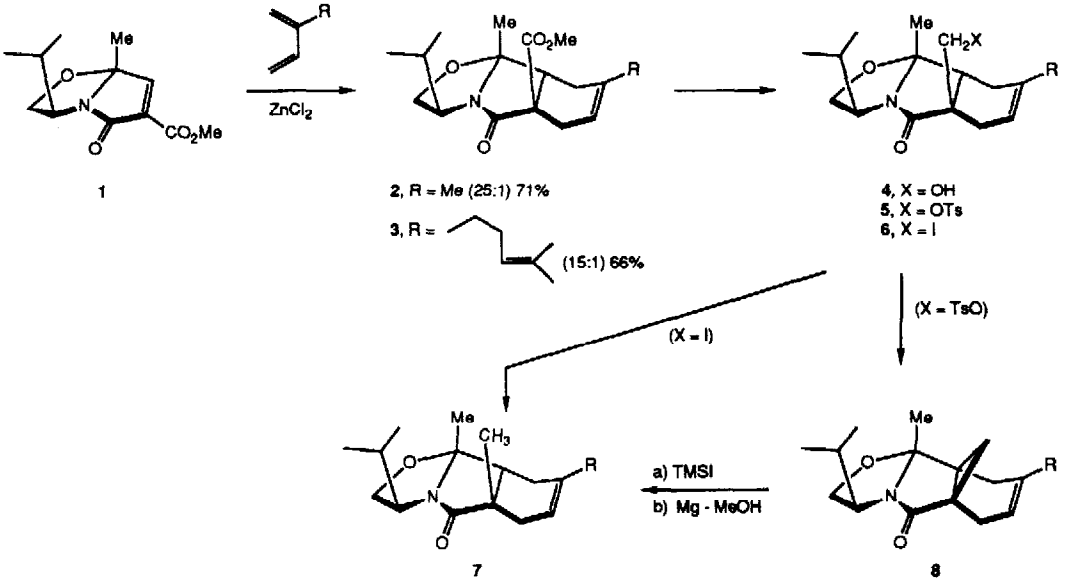
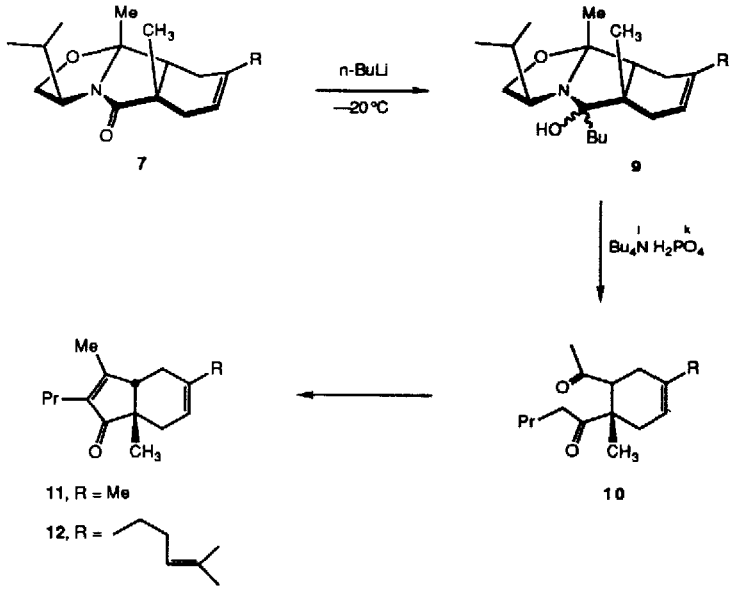
Summary: The cycloadducts from Diels-Alder reactions have been transformed into novel functionalized carbocycles **11** and **12** in high enantiomeric excess.

In the previous Letter,[1] we have described the efficient cycloaddition of various dienes to the chiral, non-racemic lactam **1**. We now wish to describe the utility of these cycloadducts in providing novel and interesting fused carbocycles in high enantiomeric purity.

Two dienes, isoprene and myrcene, were chosen as examples to demonstrate the potential value of the process. The cycloaddition of these dienes to the lactam **1** was performed in methylene chloride (0.1 M) using 10 equiv of diene, 1.0 equiv of zinc chloride-ether (1 M, Aldrich) and stirring at 0° for 4 hrs. In this fashion, the adduct **2** was obtained in 71% yield as a 25:1 ratio of regioisomers and exclusively as the *endo* diastereomer. Furthermore, the adduct **3** was obtained in 66% yield as a 15.2:1 ratio of regioisomers and again, exclusive formation of the *endo* product was observed.[1]



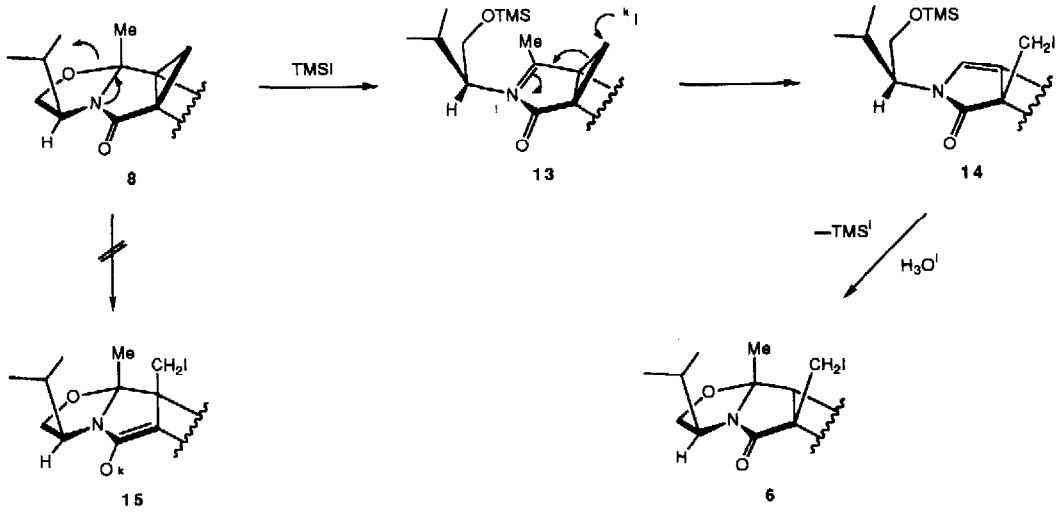
It was our intention to transform the angular carbomethoxy group to methyl in **2** and **3** and in this regard the following sequence of reactions were successfully implemented. Reduction of the carbomethoxy group in these cycloadducts was readily accomplished (95%) using sodium borohydride in ethanol at -5° to 25° and the resulting alcohol **4** was transformed into the tosylate **5** (TsCl, TEA, DMAP, 25°, 24 h, 99%). Our first attempt to hydrogenolyze the latter to the methyl group using $NaBH_4$-DMSO (80°, 9 hrs), gave, exclusively, the cyclopropyl derivative **8** in quantitative yield. This unusual rearrangement which proceeds *via* the ring opened lactam and the acyl imminium salt has already been discussed.[2] We were able to transform **8** into the angular methyl derivative **7** by treatment with trimethyl silyl iodide (-27°, CH_2Cl_2) to give the iodomethyl derivative **6**. This was followed by reduction with magnesium in methanol[3] to furnish the product in 55-60%, for the two steps. Alternatively, the tosylate **5** was converted to the iodide **6** (NaI, acetone) and transformed into the methyl derivative **7**, *via* the magnesium-methanol reduction.



The route to the carbocyclic products was completed by treatment of the lactams **7** with *n*-butyllithium at -20° to furnish the carbinolamines **9** as a mixture of diastereoisomers. The mixtures were not addressed and the crude material subjected directly to hydrolytic conditions (1.0 M $Bu_4NH_2PO_4$, EtOH, reflux, 4 hr) to give the crude diketone **10**. Without purification the diketones were added to sodium ethoxide in ethanol and stirred overnight at room temperature giving the bicyclic ketones **11**[4] and **12**[5] in 55-60% overall yield for the three steps originating from **7**. The regiochemical course of the cyclopropane ring opening in **8** deserves some further comment. It was expected that the iodide would attack the cyclopropane ring in a fashion that would lead to the enolate **15**, however, this was not the case. The very strong propensity of these bicyclic lactams to undergo reversible ring fragmentation[2] to the acyl imminium salt and trapping by TMSI to**13**, under very mild conditions (-25° to rt), most likely serves as the major driving force to the observed mode of

cyclopropane ring opening to **14**. Aqueous work-up and cleavage of the TMS group then allows for re-formation of the bicyclic lactam ring system **6**.

The two examples described herein are typical of the sorts of enantiomerically pure products that are possible from this methodology and studies are in progress for further applications.



Acknowledgement. The authors are grateful to the National Institutes of Health for financial support of this work.

References and Notes

1. Meyers, A. I.; Busacca, C. A. *Tetrahedron Lett.*, preceding paper.
2. Meyers, A. I.; Bienz, S.; Busacca, C. *J. Am. Chem. Soc.* **1989**, *111*, 1905.
3. Hutchins, R. O.; Suchismita, Abstracts of the 197th ACS Meeting, Dallas, TX; **0**-103.
4. Physical data for **11**: oil, purified by chromatography on silica gel (Amicon Matrex,® 10:1 pentane:Et_2O). ^1H NMR (270 MHz, $CDCl_3$): δ 5.39 (m, 1 H), 2.49 (m, 1 H), 2.32-1.97 (m, 6 H), 1.93 (s, 3 H), 1.70 (m, 1 H), 1.59 (s, 3 H), 1.32 (m, 2 H), 1.02 (s, 3 H), 0.77 (t, J = 7.3, 7.3 Hz, 3 H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 213.04, 169.27, 140.60, 134.70, 121.44, 51.89, 47.23, 33.55, 30.72, 24.98, 23.95, 23.11, 21.46, 14.83, 13.50. IR (film, cm^{-1}): 2961, 2933, 2872, 1694, 1644, 1447, 1383, 1353, 1333, 1311, 1186, 1058, 1050, 964, 794, 731; $[\alpha]_D$ = +19.8° (c 1.91, acetone). UV: λ_{max} 233nm (CH_3CN), ε = 10,000. **Anal.** Calcd for $C_{15}H_{22}$: C, 82.52; H, 10.16. Found: C, 82.76; H, 10.28.
5. Physical data for **12**: purified by chromatography on silica gel (Amicon Matrex,® 5:1 pentane:Et_2O). ^1H NMR (270 MHz, $CDCl_3$): δ 5.42 (m, 1 H), 500 (m, 1 H), 2.50 (m, 1 H), 2.35-1.52 (m, 10 H), 1.95 (s, 3 H), 1.63 (s, 3 H), 1.54 (s, 3 H), 1.34 (m, 2 H), 1.03 (s, 3 H), 0.79 (t, J = 7.3, 7.3 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ 212.91, 169.02, 140.69, 138.78, 131.53, 124.02,

121.18, 52.10, 47.47, 37.14, 33.36, 29.73, 26.33, 25.59, 25.08, 24.14, 21.51, 17.60, 14.86, 13.68. IR (film, cm^{-1}): 2960, 2930, 2871, 1699, 1647, 1451, 1384, 1353, 1334, 1313, 1187, 1106, 1054, 968, 759; $[\alpha]_D$ = +43.6° (c = 2.76, acetone). UV: λ_{max} 234 nm (CH_3CN), ε = 13,000. **Anal** Calcd for $C_{20}H_{30}O$: C, 83.86; H, 10.56. Found: C, 83.79; H, 10.74.

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