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Intramolecular Nitrile Oxide Cycloaddition in the Dihydrotropone Series. A Rapid Entry into the Bicyclo[5.3.0]decane and Bicyclo[5.4.0]undecane Ring Systems

James H. Rigby* and Timothy W. McGuire

Department of Chemistry
Wayne State University
Detroit, Michigan 48202

Summary: 1,8-Addition of terminally functionalized three and four carbon chains to tropone followed by intramolecular nitrile oxide cycloaddition provides highly functionalized bicyclo[5.3.0]decane and bicyclo[5.4.0]undecane products.

2,4,6-Cycloheptatrien-1-one (tropone) has emerged as a versatile building-block for the construction of a wide-range of polycyclic systems possessing seven-membered carbocycles.[1] In connection with some synthetic studies currently underway in our laboratory, a functionalized cis-hydroazulene intermediate amenable to stereocontrolled carbon bond installation specifically on the concave surface of the cycloheptane moiety was required. In light of the well-known conformational ambiguities associated with flexible seven-membered rings,[2] it was reasoned that construction of a rigid hydroazulene precursor would ensure strict control of relative stereochemistry in the carbocyclic product. The hydroazulene synthesis previously reported from our laboratory featuring a Lewis acid promoted intramolecular hetero-Diels-Alder reaction is particularly well-suited for producing species susceptible to exo-face manipulation[3] A strategy that retains the advantages of executing carbon bond formation on the tropone nucleus while permitting access to alternative stereochemical arrangements would enhance the utility and versatility of this general methodology. A straightforward approach for addressing some of these issues is presented in this letter.

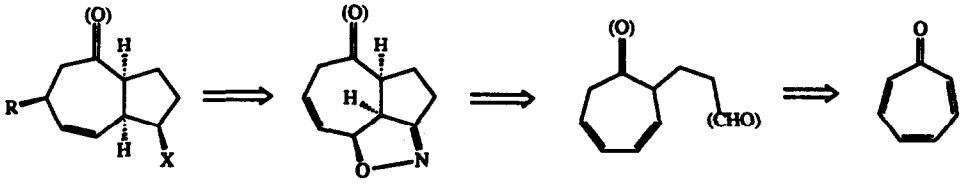
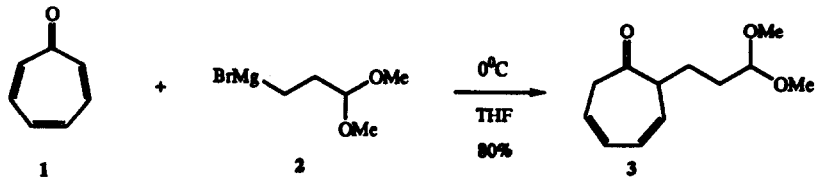


Figure 1

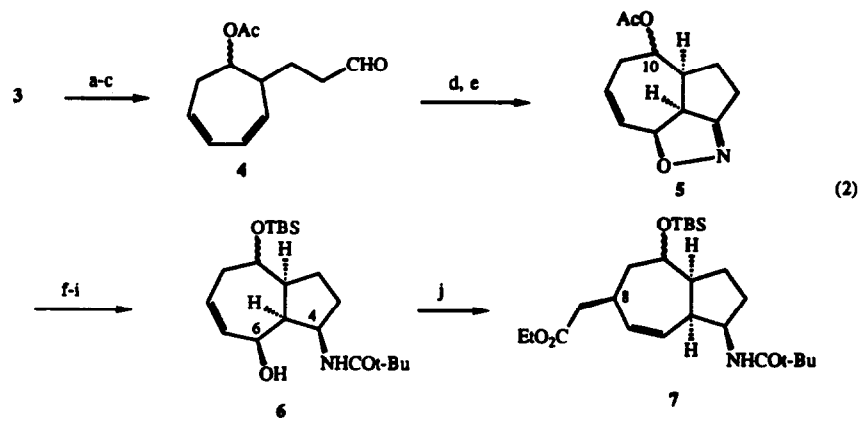
It was envisioned that a sequence commencing with a 1,8-addition of an appropriately functionalized three-carbon chain to tropone followed by an intramolecular nitrile oxide cycloaddition would deliver a carbocyclic framework exhibiting functionality suitably disposed for subsequent chemical operations on the endo-face of the resultant bicyclic system (Figure 1).[4] Nitrile oxide cycloaddition chemistry has been exploited

previously for the synthesis of hydroazulene systems. Kozikowski and co-workers reported a strategy in which a seven-membered ring was installed onto an existing cyclopentane ring via a nitrile oxide cycloaddition[5] and in connection with a synthesis of biotin, Confalone and co-workers explored a heteroatom version of the cyclopentannulation strategy starting from cycloheptene.[6] Furthermore, Wender employed a related cycloaddition in a construction of the phorbol AB ring.[7]



1 2 3 (1)

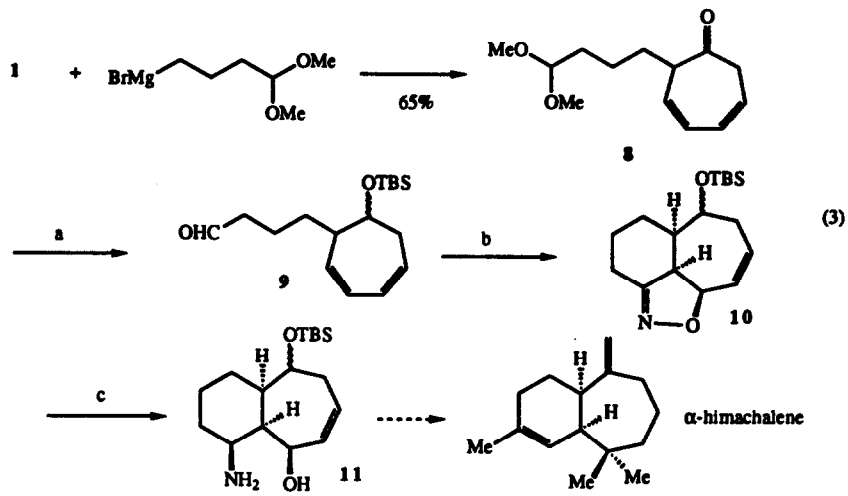
In the current investigation, addition of the Grignard reagent derived from 1-bromo-3,3-dimethoxypropane (2)[8] to tropone in a 1,8-fashion provided the key dihydrotropone 3[9] in 80% yield.[1,3] Reduction of the ketone in 3 followed by acetylation and careful hydrolysis of the dimethoxy acetal led to aldehyde 4 (3:1 cis/trans isomer mixture).[9] This material was converted into the corresponding oxime which underwent spontaneous room temperature [3+2] cycloaddition with the proximate alkene upon oxidation to the corresponding nitrile oxide with a dilute solution of sodium hypochlorite.[10] The anticipated isoxazoline 5[9] was obtained in 90% yield as a 3:1 mixture of C_{10} epimers. Routine functional group manipulation afforded the amino-alcohol derivative 6,[9] which exhibited a handle in the cycloheptene moiety suitable for stereoselective introduction of the requisite carbon substituent at C_8 (Equation(2)).[11] This important feature of intermediate 6 was demonstrated by effecting a simple Claisen rearrangement with triethyl orthoacetate to afford compound 7.



a) $NaBH_4$/MeOH, 0°C (95%) b) Ac_2O/TEA, CH_2Cl_2, 0°C (95%) c) 5% aq. TFA, (87%) d) $NH_2OH{\cdot}HCl$, TEA, RT (70%) e) 5% NaOCl, CH_2Cl_2, RT (90%) f) K_2CO_3(aq), MeOH (98%) g) TBSCl, imidazole, DMF (95%) h) $LiAlH_4$, 0°C (70%) i) $(CH_3)_3CC(O)Cl$, TEA, DMAP, 0°C (80%) j) $(EtO)_3CCH_3$, CSA (30%)

While nitrile oxide cycloaddition technology easily solved the stereochemical problems encountered in the hydroazulene series, application to a more intractable obstacle was then investigated. A significant limitation of

our previously described intramolecular Lewis acid mediated hetero-Diels-Alder protocol was the inability to extend the cyclization chemistry to other systems.[3a,b] For example, the reaction failed with side-chains longer than three carbons,[12] nevertheless, assembly of the cis-fused bicyclo[5.4.0]undecane ring system characteristic of the himachalene sesquiterpenes by this method is quite appealing. It was envisaged that the tandem 1,8-addition-intramolecular nitrile oxide cycloaddition sequence could offer advantages over previous chemistry that would permit efficient construction of functionalized cis-fused bicyclic systems of this type.



a) *i.* $NaBH_4$/MeOH *ii.* TBDMSCl, imidazole *iii.* TFA, aq. acetone (36%) b) i. NH_2OH HCl, TEA ii. $NaOCl/CH_2Cl_2$ (56%) c) $LiAlH_4/Et_2O$ (95%)

In the event, treatment of tropone (**1**) with the corresponding four-carbon Grignard reagent[13] provided the homologated side-chain substituted dihydrotropone **8**[9] in 65% yield. Routine oxidation level adjustment and protecting group manipulation in a fashion similar to that performed in the hydroazulene series provided the nitrile oxide precursor **9**[9] that was then exposed to hydroxylamine hydrochloride under standard conditions. Conversion of the resultant oxime to the nitrile oxide by oxidation with sodium hypochlorite proceeded without incident and cycloaddition ensued immediately. To our delight, the cis-fused bicyclic product **10**[9] was isolated in 56% yield for the two steps. Reductive cleavage of the isoxazoline ring followed uneventfully to afford the amino alcohol **11** which displays a pattern of functionality appropriate for conversion into the sesquiterpene α-himachalene.[14] The successful installation of six-membered carbocycles onto the tropone nucleus greatly expands the utility of the tandem 1,8-addition-intramolecular cycloaddition protocol for construction of polycyclic systems possessing seven-membered rings and solves a long standing problem in this area.

The use of intramolecular nitrile oxide cycloaddition chemistry provides a stereocomplementary alternative to previous entries into the cis-hydroazulene system as well as offering solutions to synthetic problems not easily addressed by the intramolecular Lewis acid mediated hetero Diels-Alder cycloaddition previously reported from this laboratory. Selection of the appropriate cycloaddition protocol at the advanced

aldehyde stage now permits the construction of bicyclic systems with a wide range of stereochemical and ring size options not previous available. Work is currently underway to apply this chemistry to the synthesis of several natural products including α-himachalene.

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References and Notes

1. Rigby, J.H. in "Studies in Natural Products Chemistry" Rahman, A.-u. Ed., Vol. 1 (Part A), Elsevier, Amsterdam, 1988, pp. 545-576.

2. a) Hendrickson, J.B. *J. Am. Chem. Soc.* **1961**, *83*, 4537. b) Hendrickson, J.B. *Tetrahedron* **1963**, *19*, 1387. c) Toromanoff, E. *Ibid.* **1980**, *36*, 2809. d) DeClercq, P.J. *Ibid.* **1981**, *37*, 4277. e) DeClercq, P.J. *Ibid.* **1984**, *40*, 3717.

3. a) Rigby, J.H. *Tetrahedron Lett.* **1982**, *23*, 1863. b) Rigby, J.H.; Wilson, J.Z. *J. Am. Chem. Soc.* **1984**, *106*, 8217. c) Rigby, J.H.; Senanayake, C. *Ibid.* **1987**, *109*, 3147.

4. For a recent overview of nitrile oxide cycloaddition, see: Wade, P.A. in "Comprehensive Organic Synthesis" Trost, B.M.; Fleming, I., Eds., Vol. 4, Pergamon Press, Oxford, 1991, pp. 1124-1133.

5. Kozikowski, A.P.; Mugrage, B.B.; Wang, B.C.; Xu, Z.-G. *Tetrahedron Lett* **1983**, *24*, 3705.

6. Confalone, P.N.; Pizzolato, G.; Confalone, D.L.; Uskokovic, M.R. *J. Am. Chem. Soc.* **1980**, *102*, 1954.

7. a) Wender, P.A.; Lee, H.Y.; Wilhelm, R.S.; Williams, P.D. *J. Am. Chem. Soc.* **1989**, *111*, 8954. b) Wender, P.A.; Kogen, H.; Lee, H.Y.; Munger, J.D., Jr.; Wilhelm, R.S.; Williams, P.D. *Ibid.* **1989**, *111*, 8957.

8. Battersby, A.R.; Buckley, D.G.; Staunton, J.; Williams, P.J. *J. Chem. Soc., Perkin Trans I*, **1979**, 2550.

9. This compound exhibited spectral (^{1}H NMR, ^{13}C NMR, IR) and analytical (HRMS) consistent with the assigned structure.

10. a) Houk, K.N.; Moses, S.R.; Wu, Y.-D.; Rondan, N.G.; Jäger, V.; Schole, R.; Fronczek, F.R. *J. Am. Chem. Soc.* **1984**, *106*, 3880. b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Gennari, C.; Raimondi, L. *J. Org. Chem.* **1987**, *52*, 4674.

11. The cis disposition of the C_4 and C_6 substituents in this series was established by conversion of the parent amino alcohol to a cyclic carbamate. (For a related stereochemical result, see ref. 6.)

12. Lee, Joung, Wayne State University unpublished results.

13. Vedejs, E.; Arnest, M.J.; Hagen, J.P. *J. Org. Chem.* **1979**, *44*, 3230.

14. For other approaches to the himachalene system, see: a) Wenkert, E.; Naemura, K. *Synth. Commun.* **1973**, *3*, 45. b) Mehta, G.; Kapoor, S.K. *J. Org. Chem.* **1974**, *39*, 2618. c) Piers, E.; Ruediger, E.H. *J. Chem. Soc., Chem. Commun.* **1979**, 166. d) Liu, H.-J.; Browne, E.N.C. *Can. J. Chem.* **1981**, *59*, 601. e) Rigby, J.H.; Sage, J.-M.; Raggon, J. *J. Org. Chem.* **1982**, *47*, 4815.

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