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β-Siloxy Unsaturated Nitriles: Stereoselective Cyclizations to *cis*- and *trans*-Decalins

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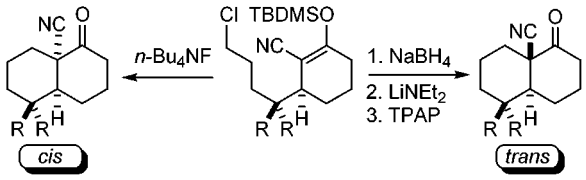
ABSTRACT

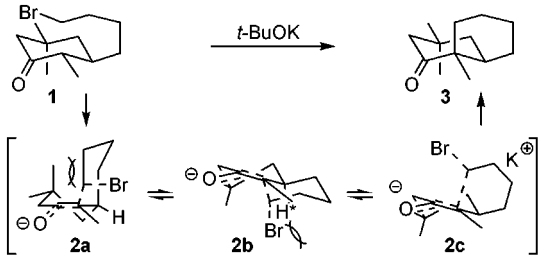


β-Siloxy unsaturated nitriles are excellent precursors to enolate and nitrile anions that cyclize to *cis*- and *trans*-decalins, respectively. The stereoelectronic requirements of endocyclic enolates and exocyclic nitrile anions are complementary, providing *cis*- and *trans*-decalins from a common intermediate. This cyclization allows the synthesis of diastereomeric *cis*- and *trans*-decalins containing a contiguous array of quaternary–tertiary–quaternary stereocenters.

cis- and *trans*-decalins are among the most prevalent structural units contained within natural products.[1] A long-standing challenge in decalin synthesis[2] is the cyclization of a single synthetic intermediate common to both *cis*- and *trans*-decalins. Historically, *cis*-decalins have been particularly common intermediates through their equilibration to the less accessible *trans*-decalins,[3] although equilibration is strongly dependent on the substitution pattern[4] and necessarily requires an epimerizable ring junction. This indirect equilibration route to *trans*-decalins is a direct stereochemical consequence of intramolecular ketone enolate alkylations that afford *cis*-decalones exclusively.

Several cleverly devised cyclizations[5] demonstrated that intramolecular alkylations of ketone enolates are kinetically controlled (Scheme 1). Of the three possible transition states for cyclization, **2a** is significantly destabilized by a severe 1,3-diaxial interaction, while **2b**, leading to a *trans*-decalin, was presumed to be destabilized by steric compression between the large bromine atom and the adjacent axial proton (H*). Alkylation therefore occurs through transition state **2c**, affording **3**.

Scheme 1



In stark contrast to enolate cyclizations, nitrile anions are unique in cyclizing to either *cis*- or *trans*-decalins,[6] depending on the nature of the metal cation (Scheme 2).[7] Unraveling

(1) (a) Glasby, J. S. In *Encyclopedia of the Terpenoids*; Wiley: Chichester, U.K., 1982. For more recent examples, see the following. (b) For sesquiterpenoids: Fraga, B. M. *Nat. Prod. Rep.* **1999**, *16*, 21. (c) For diterpenoids: Hanson, J. R. *Nat. Prod. Rep.* **1999**, *16*, 209. (d) For triterpenoids: Connolly, J. D.; Hill, R. A. *Nat. Prod. Rep.* **1999**, *16*, 221.

(2) For an excellent summary of decalin syntheses see: Vandewalle, M.; DeClercq, P. *Tetrahedron* **1985**, *41*, 1767.

(3) Heathcock, C. H. In *The Total Synthesis of Natural Products*; ApSimon, J. Ed.; Wiley: New York, 1973; Vol. 2, pp 197−558.

(4) Thompson, H. W.; Long, D. J. *J. Org. Chem.* **1988**, *53*, 4201.

(5) Conia, J.-M.; Rouessac, F. *Tetrahedron* **1961**, *16*, 45.

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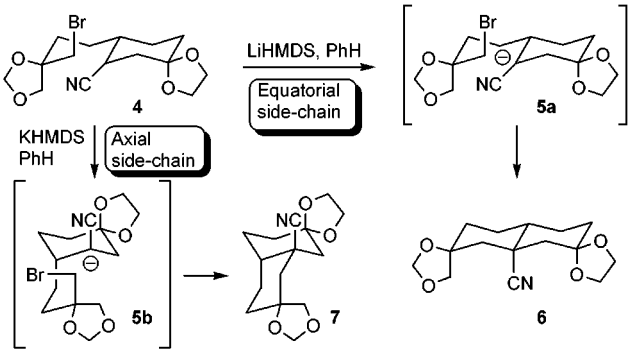
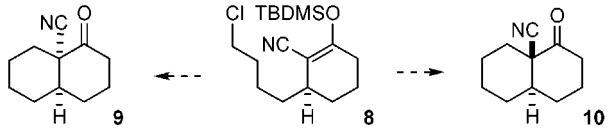
Scheme 2



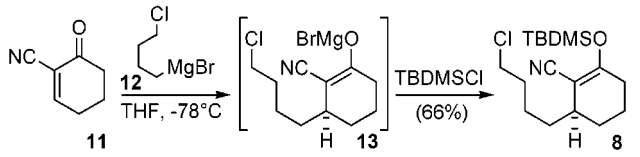
this unprecedented cation effect led to the discovery that the side chain orientation controls the alkylation stereochemistry, with equatorially oriented substituents affording *trans*-decalins (**4** → **6**) and axially oriented substituents providing *cis*-decalins (**4** → **7**). This pioneering nitrile anion cyclization has been underappreciated,[8] possibly because of a perceived substrate specificity and the reversal of stereoselectivity observed with differing counterions, raising questions about the predictability and generality of the cyclization.

Our aim has been to synthesize functionalized β-siloxy unsaturated nitriles[9] (**8**) for stereoselective cyclizations to *cis*- and *trans*-decalins. Conceptually, β-siloxy unsaturated nitriles allow generation of either ketone enolates or nitrile anions, providing a potential means of stereocontrol in alkylations with an appropriately positioned electrophile. Realizing this goal would not only facilitate decalin syntheses but contribute to the fundamental understanding of intramolecular ketone enolate and nitrile anion alkylations.



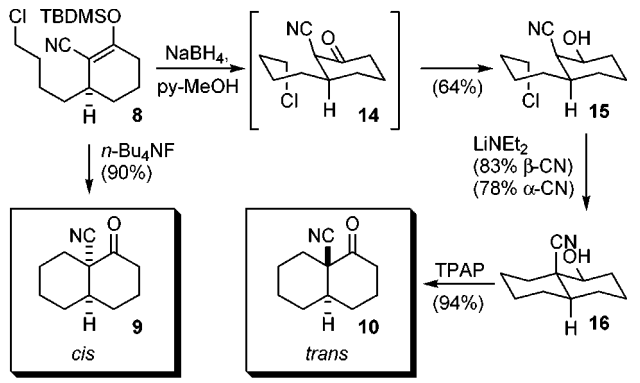
The uncatalyzed conjugate addition of Grignard reagents to the unsaturated oxonitrile **11**[10] provides an extremely concise route to β-siloxy unsaturated nitriles.[9] Reacting the chlorobutyl Grignard reagent **12**[11] with **11** results in a smooth conjugate addition, affording an intermediate enolate that reacts with TBDMSCl[12] to provide the β-siloxy unsaturated nitrile **8** (Scheme 3). Interception of the enolate as the silyl ether is particularly important in allowing the subsequent conversion of **8** to a nitrile anion while avoiding a premature cyclization of enolate **13**.

Scheme 3



Cyclization of **8** to the *cis*-decalin **9** parallels the known intramolecular alkylations of ketone enolates.[13] Enolate formation and alkylation of **8** occurs smoothly upon addition of *n*-Bu_4NF, providing a single *cis*-decalin **9** whose structure was secured by X-ray analysis[14] (Scheme 4). Attention was

Scheme 4



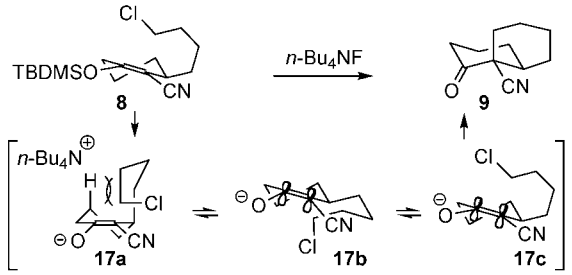
then focused on cyclizing the corresponding nitrile anion to the diastereomeric *trans*-decalin. The requisite nitrile **15** was prepared in a one-pot reaction[15] involving sequential silyl ether cleavage, protonation of the intermediate enolate, and reduction of the resulting ketone (3:2 ratio of β to α nitrile epimers). Exposing the individual β-hydroxy nitriles **15** to excess $LiNEt_2$ results in an efficient cyclization to a single diastereomeric decalin **16**. Oxidation[16] of **16** provides the crystalline *trans*-decalin **10**, whose structure was unequivocally determined by X-ray analysis.[14]

The ketone enolate and nitrile anion cyclizations of **8** and **15** provide diastereomeric *cis*- and *trans*-decalins from a common intermediate. We believe that this complementary stereoselectivity is caused by different orbital alignments of ketone enolates and nitrile anions. Endocyclic ketone enolates

(6) Stork, G.; Gardner, J. O.; Boeckman, R. K., Jr.; Parker, K. A. *J. Am. Chem. Soc.* **1973**, *95*, 2014.
(7) Stork, G.; Boeckman, R. K., Jr. *J. Am. Chem. Soc.* **1973**, *95*, 2016.
(8) No examples of *trans*-selective cyclizations were found from a Science Citation search of ref 7.
(9) Fleming, F. F.; Pu, Y.; Tercek, F. *J. Org. Chem.* **1997**, *62*, 4883.
(10) Fleming, F. F.; Huang, A.; Sharief, V. A.; Pu, Y. *J. Org. Chem.* **1997**, *62*, 3036.
(11) Bernady, K. F.; Poletto, J. F.; Nocera, J.; Mirando, P.; Schaub, R. E.; Weiss, M. J. *J. Org. Chem.* **1980**, *45*, 4702.
(12) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462.
(13) Vite, G. D.; Spencer, T. A. *J. Org. Chem.* **1988**, *53*, 2560. (b) Piers, E.; Yeung, B. W. A. *J. Org. Chem.* **1984**, *49*, 4567. (c) Posner, G. H.; Sterling, J. J.; Whitten, C. E.; Lentz, C. M.; Brunelle, D. J. *J. Am. Chem. Soc.* **1975**, *97*, 107.
(14) The authors have deposited atomic coordinates with the Cambridge Crystallographic Data Center. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, U.K.
(15) Rhodes, R. A.; Boykin, D. W. *Synth. Commun.* **1988**, *18*, 681.
(16) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.
(17) Eliel, E. L.; Wilen, S. H.; Mander, L. N. In *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 696−697.

can only access two conformations, **17a** and **17c**, in which the π-electrons of the enolate are aligned with the electrophilic chloromethylene carbon for an S_N2 displacement (Scheme 5). This alignment is not possible in **17b**, where

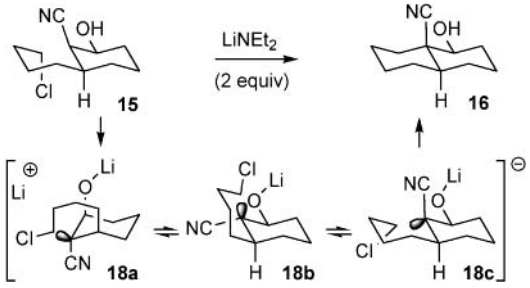
Scheme 5



the π-electrons of the enolate incline away from the carbon−chlorine bond, preventing alkylation from conformer **17b**, even though **17b** is sterically more favorable than **17c**. Formation of the *cis*-decalin **9** is therefore stereoelectronically controlled by the orbital alignment of the endocyclic ketone enolate.

In contrast to ketone enolates, nitrile anions exhibit unique stereoselectivities,[7] reflecting both the extremely small size of the nitrile group[17] and the exocyclic nature of the anion. These features are apparent in the conformations **18a**−**c**, where both six-membered rings can adopt full chair conformations (Scheme 6), unlike the corresponding enolate.[18]

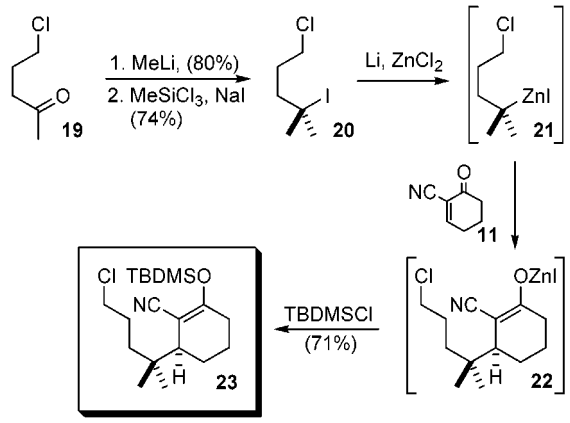
Scheme 6



Excellent orbital overlap is achieved in all three conformations, since the nitrile anion is directly oriented toward the electrophilic chloromethylene carbon. Alkylation preferentially occurs from conformation **18c**, in which the equatorial orientation of both the chlorobutyl chain and the forming bond minimizes the syn-axial steric interactions.[19] The stereoselectivity therefore results from the exocyclic nature of the nitrile anion.[20]

We have extended this cyclization strategy to the synthesis of 1,1-*gem*-dimethyl-substituted decalins that are commonly found in a large number of terpenoids.[1] Installation of the *gem*-dimethyl group required access to a novel organometallic reagent (**21**) that was prepared from **19** by sequential methylation, iodination,[21] and zincation (Scheme 7). Treating

Scheme 7



20 with Rieke zinc[22] results in the selective metalation of the carbon−iodine bond, providing an organozinc reagent that reacts smoothly with **11** and TBDMSCl to provide the β-siloxy unsaturated nitrile **23**. This conjugate addition proceeds in excellent yield (71%), particularly considering the steric bulk of the nucleophile, and represents the first example of a noncatalyzed, organozinc addition to a β-oxo-α,β-unsaturated nitrile.[23]

Cyclizing the β-siloxy unsaturated nitrile **23** through the corresponding enolate and nitrile anions selectively provides either the *cis*- or *trans*-dimethyl-substituted decalins. Fluoride-induced cleavage of **23** generates an intermediate enolate that cyclizes exclusively to the *cis*-decalin **24** (Scheme 8). Formation of the diastereomeric *trans*-decalin requires cyclization of the corresponding nitrile **26**, which is prepared by reduction of **23** with $NaBH_4$.[15] Cyclization of **26** occurs smoothly with excess lithium diethylamide, providing the *trans*-decalin **27**, regardless of the nitrile orientation in the

(18) The anion is shown as an sp^3-hybridized, inductively stabilized anion reflecting the product-like character of the transition state. The exact hybridization of nitrile anions is the subject of considerable discussion. For leading references see: (a) Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Corset, J.; Castella-Ventura, M.; Froment, F. *J. Org. Chem.* **1998**, *63*, 3287. (b) Koch, R.; Wiedel, B.; Anders, E. *J. Org. Chem.* **1996**, *61*, 2523. (c) Wiberg, K. B.; Castejon, H. *J. Org. Chem.* **1995**, *60*, 6327. (d) Carlier, P. R.; Lucht, B. L.; Collum, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 11602. (e) Abbotto, A.; Bradamante, S.; Pagani, G. A. *J. Org. Chem.* **1993**, *58*, 449.

(19) A related equatorial alkylation of nitrile anions was recently observed in a clever double-Michael reaction: Grossman, R. B.; Varner, M. A.; Skaggs, A. J. *J. Org. Chem.* **1999**, *64*, 340.

(20) The equatorial orientation of the alkoxide intermediate has a profound effect on the stereoselectivity since the cyclization of the corresponding axial alcohol, obtained as a minor component in the reduction of **10**, affords the *cis*-decalin. We speculate that an axial alkoxide causes twisting of the cyclohexane ring, preventing sufficient orbital alignment in **20c** and favoring alkylation from **20b**. We are currently examining this stereoselectivity with the *des*-hydroxy analog.

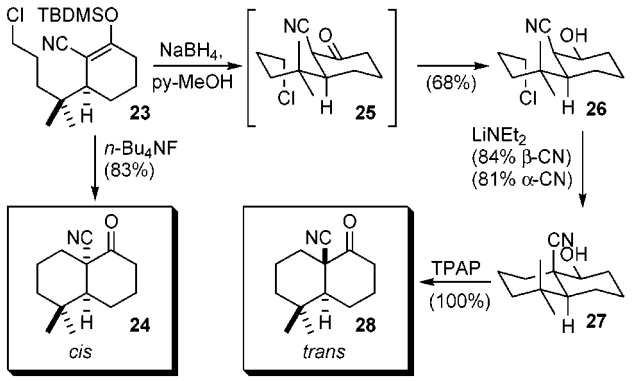
(21) Olah, G. A.; Husain, A.; Singh, B. P.; Mehrotra, A. K. *J. Org. Chem.* **1983**, *48*, 3667.

(22) Zhu, L.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445.

(23) For the addition of tertiary organozinc bromides to enones see: Hanson, M. V.; Rieke, R. D. *J. Am. Chem. Soc.* **1995**, *117*, 10775.

(24) The identity of the two crystalline decalones was secured by X-ray analysis.

Scheme 8



hydroxy nitrile **26**. This cyclization leads exclusively to the *trans*-decalin **27** and simultaneously installs the hindered quaternary center with complete stereocontrol. Oxidation[16] of **27** provides the *trans*-decalin **28**, that differs from **24** only in the ring junction stereochemistry.[24]

The addition of functionalized Grignard and organozinc reagents to α,β-unsaturated oxonitriles provides an extremely simple route to diastereomeric *cis*- and *trans*-decalins from a common β-siloxy unsaturated nitrile. This addition−cyclization strategy not only allows complementary stereoselectivity in intramolecular alkylations but also installs a contiguous array of quaternary−tertiary−quaternary stereocenters commonly found in many terpenoids. Collectively these cyclizations demonstrate the fundamental stereoelectronic requirements inherent in ketone enolate and nitrile anion cyclizations.

Acknowledgment. Financial support from the NIH is gratefully acknowledged. Shih-Chi Chang is thanked for assistance with the X-ray structure determinations.

Supporting Information Available: X-ray structures of **9** and **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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