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Cis and Trans Selective 1,4-Addition of a Lithium Dithioester Enolate to 4-*O*-TBS-2-cyclohexenone

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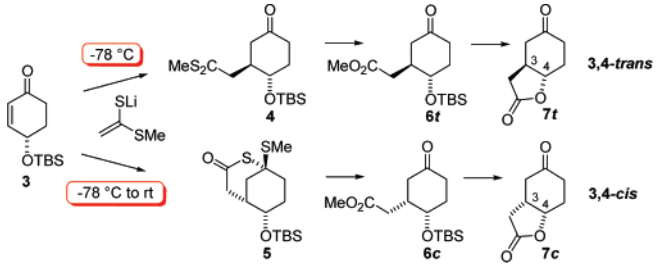
ABSTRACT



The 1,4-addition of the lithium enolate of methyldithioacetate (LMDTA) to (±)-4-*O*-TBS-2-cyclohexenone (3) can be varied from being highly 3,4-trans selective to being highly 3,4-cis selective simply by varying the reaction temperature. This stereodivergency allows expedient syntheses of the corresponding trans and cis methyl esters 6t and 6c and derived bicyclic ketolactones 7t and 7c.

The 1,4-addition of carbon-based nucleophiles to 2,3-unsaturated carbonyl compounds constitutes a powerful C−C bond forming reaction for synthesis.[1] 4-Substituted 2-cyclohexenones are a particularly well-studied class of substrates because the enolates generated by these reactions have found widespread use in target orientated synthesis.[2] Control of the relative stereochemistry between C3 and C4 and the ability to trap the enolates with electrophiles at oxygen or stereoselectively at C2 is critical for maximum versatility.

The most widely studied classes of *C* nucleophiles are organocopper, higher order (HO) cuprate, and lower order (LO) cuprate reagents.[1] These reagents all react with high levels of 3,4-trans selectivity for 4-substituted 2-cyclohexenones.[3] The origin of the trans selectivity has been attributed to initial reversible formation of diastereomeric d−π* Cu(III) complexes followed by preferential insertion by the trans complex on steric grounds.[4] The enolates formed from organocopper additions (e.g., using $RCu{\cdot}BF_3$) are rather unreactive toward electrophile trapping reactions,[5] but the enolates resulting from HO and LO cuprate additions generally participate efficiently.[6]

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(1) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, U.K., 1992.

(2) Lopez-Pelegrin, J. A.; Janda, K. D. *Chem.—Eur. J.* **2000**, *6*, 1917−1922 and references therein.

(3) The situation for substrates containing a quaternary *C*- and *O*-substituted 4-stereocenter is more complex: 1,4-addition of Me_2CuLi/Et_2CuLi to cyclohexenone γ-spiroacetal gave cis selectivity relative to the *O*-substituent in the absence of TMSCl but trans selectivity in the presence of TMSCl. See ref 4a and Jameleddine, K.; Yakdhan, K.; Jamil, K.; Bechir, B. H.; Denis, G. *Synth. Commun.* **2002**, *32*, 2719−2722.

(4) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015−6018. (b) Hareau-Vittini, G.; Hikichi, S.; Sato, F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2099−2101.

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(6) (a) McMurray, J. E.; Scott, W. J. *Tetrahedron Lett.* **1983**, *24*, 979−982. (b) Polniaszek, R. P.; Dillard, L. W. J. *Org. Chem.* **1992**, *57*, 4103−4110. (c) Comins, D. L.; Dehghani, A. *Tetahedron Lett.* **1992**, *33*, 6299−6302. (d) Comins, D. L.; Al-awar, R. S. *J. Org. Chem.* **1995**, *60*, 711−716.

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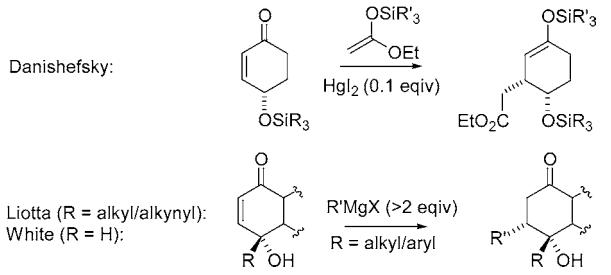
By contrast, just two cis selective 1,4-addition protocols for 4-substituted 2-cyclohexenones have been developed.[7] The first was Danishefsky et al.'s HgI_2 catalyzed cis addition of silyl ketene acetals to 4-*O*-siloxy-2-cyclohexenones,[8] and the second was Liotta et al.'s Mg−alkoxide promoted cis-addition of alkyl and aryl Grignard reagents to 4-hydroxy-2-cyclohexenones.[9] The Liotta method was originally developed for substrates having a *tert*-hydroxyl directing group but has subsequently been used by White with a *sec*-hydroxyl directing group[10] (Scheme 1).

Scheme 1. Stereoselective Conjugate Addition Reactions to Cyclic 4-Alkoxy Enones



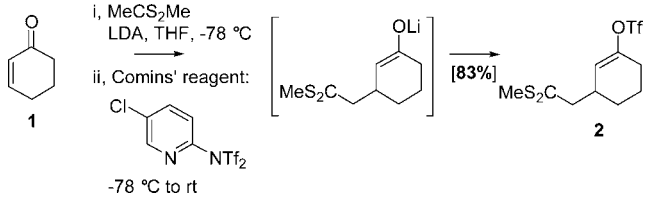
Danishefsky et al. ascribed the cis selectivity in their silyl ketene acetal additions to stereoelectronically controlled attack anti to the best σ donor (i.e., σ_{CH} not σ_{CO}).[8c,11] Swiss and Liotta proposed association of the nucleophile with hydroxy function then intramolecular delivery in their protocol.[9b]

In connection with a total synthesis program directed toward the synthesis of Amaryllidaceae alkaloids[12] we were interested in developing a method for cis selective 1,4-addition of a functionalized 2-carbon nucleophile to a 4-*O*-TBS-2-cyclohexenone under conditions which would allow for the trapping of the resulting enolate at oxygen as the vinyl triflate. Neither of the aforementioned methods proved suitable so we sought to develop a new protocol.

Metzner has shown that lithium dithioester enolates undergo smooth 1,4-addition to a range of enones[13] including trans selective 1,4-addition (dr 94:6) to 4-methyl-2-cyclohexenone.[14] We envisaged that the high oxaphilicity of Li might result in cis selective addition to 4-alkoxy enones by analogy with the proposed role of Al in some cis selective additions of alkynyl and trialkyl aluminum reagents to 3-alkoxy-2-cyclopentenones.[15]

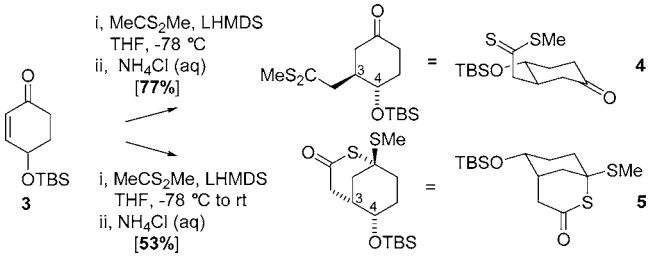
Preliminary experiments established that the lithium enolate of methyldithioacetate (LMDTA) underwent smooth 1,4-addition to 2-cyclohexenone (**1**) in THF at −78 °C and that the resulting enolate could be trapped using Comins' reagent to give the vinyl triflate **2** in 83% yield (Scheme 2).

Scheme 2. 1,4-Addition of LMDTA to 2-Cyclohenenone (**1**) and Trapping with Comins' Reagent



Applying the same conditions but using (±)-4-*O*-TBS-2-cyclohexenone (**3**) as the substrate and initially quenching with aqueous NH_4Cl we were intrigued to find that two isomeric products **4** and **5** were formed exclusively depending on whether the reactions were quenched at −78 °C or after warming to room temperature, respectively (Scheme 3).

Scheme 3. 1,4-Addition of LMDTA to (±)-4-*O*-TBS-2-cyclohexenone (**3**)—NH_4Cl Quench at −78 °C and after Warming to Room Temperature



As we were unable to establish the relative stereochemistries between C3 and C4 in the products **4** and **5** by NOE measurements, the stereochemical assignments for these products were established by conversion to the novel trans ketolactone **7t** and the known cis ketolactone **7c**, respectively. This involved HgO-mediated[16] conversion to the isomeric

(7) More recently, Yamazaki reported that 1,4-addition of the potassium enolate of cyanoethyl acetate to enone **3** proceeded with moderate cis selectivity (dr 73:22); no rationale was proposed: Yamazaki, N.; Kusangagi, T.; Kibayashi, C. *Tetahedron Lett.* **2004**, *45*, 6509−6512.

(8) (a) Danishefsky, S. J.; Simoneau, B. *Pure Appl. Chem.* **1988**, *60*, 1555−1562. (b) Danishefsky, S. J.; Simoneau, B. *J. Am. Chem. Soc.* **1989**, *111*, 2599−2604. (c) Jeroncic, L. O.; Cabal, M. P.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 387−395.

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(12) Rinner, U.; Hudlicky, T. *Synlett* **2005**, 365−387.

(13) (a) Metzner, P. *Synthesis* **1992**, 1185−1199. (b) Berrada, S.; Desert, S.; Metzner, P. *Tetrahedron* **1988**, *44*, 3575−3586. (c) Berrada, S.; Metzner, P.; Rakotonirina, R. *Bull. Soc. Chim. Fr.* **1985**, 881−890.

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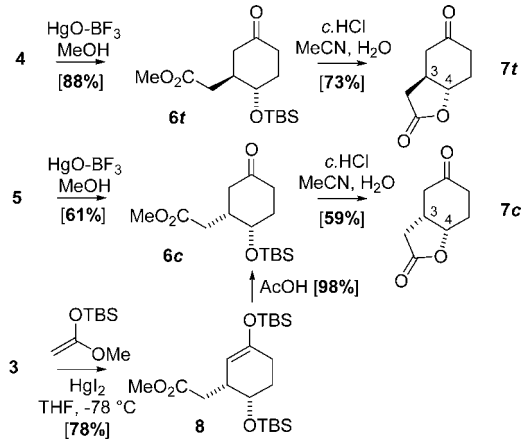
(15) (a) Pappo, R.; Collins, P. W. *Tetahedron Lett.* **1972**, 2627−2630. (b) Collins, P. W.; Dajani, E. Z.; Bruhn, M. S.; Brown, C. H.; Palmer, J. R.; Pappo, R. *Terahedron Lett.* **1975**, 4217−4220. (c) Collins, P. W.; Dajani, E. Z.; Driskill, D. R.; Bruhn, M. S.; Jung, C. J.; Pappo, R. *J. Med. Chem.* **1977**, *20*, 1152−1159. (d) Caddick, S.; Delisser, V. M. *Terahedron Lett.* **1997**, *38*, 2355−2358. (e) Yakura, T.; Tanaka, K.; Iwamoto, M.; Nameki, M.; Ikeda, M. *Synlett* **1999**, 1313−1315. (f) Yakura, T.; Tanaka, K.; Kitano, T.; Uenishi, J.; Ikeda, M. *Tetrahedron* **2000**, *56*, 7715−7721.

(16) Jung, M. E.; Parker, M. H. *J. Org. Chem.* **1997**, *62*, 7094−7095.

methyl esters **6t** and **6c**[17] and then acid mediated TBS deprotection/lactonization[18] (Scheme 4).

Scheme 4. Confirmation of Relative Stereochemistry (at C3 and C4) for Products **4** and **5**



The identity of trans ketolactone **7t** was secured with a single-crystal X-ray structure determination (Figure 1 and

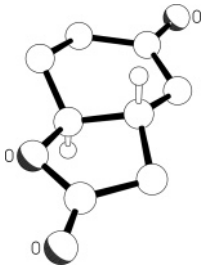


Figure 1. Molecular structure of trans ketolactone **7t**.

Supporting Information) whereas the identity of cis ketolactone **7c** was confirmed by re-synthesis according to the method of Danishefsky (**3** → **8** → **6c** → **7c**)[19] and also comparison with Danishefsky's published data.[8c]

Additionally, the relative stereochemistry and identity of cis addition product **5** was unambiguously established by a single-crystal X-ray structure determination (Figure 2 and Supporting Information).[20]

(17) Interestingly, trans TBS ether **6t** is very prone to desilylation on silica to give the corresponding alcohol whereas cis TBS ether **6c** is not. The trans alcohol can, however, also be readily cyclized to trans lactone **7t** (68%); see Supporting Information.

(18) TBS ether deprotection/lactonization was performed essentially as in ref 8c but using HCl in place of HF.

(19) We used $CH_2C(OMe)OTBS$ rather than $CH_2C(OEt)OTBS$ and, therefore, obtained the Me ester (cf. Et ester in ref 8c).

(20) Compound **5** crystallized with two independent molecules (**I** and **II**) in the asymmetric unit; molecule **I** is shown in Figure 2, and molecule **II** is shown in Figure S2 in the Supporting Information. The two molecules have essentially identical geometries (excluding the disorder in molecule **II**—see the Supporting Information) as can be seen by comparing the two images.

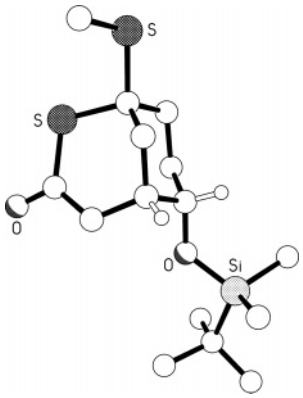
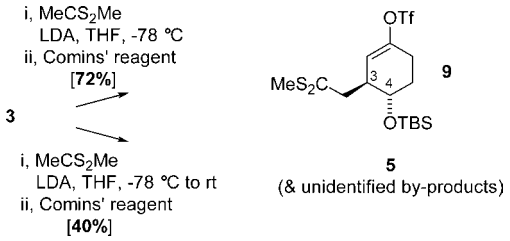


Figure 2. Molecular structure of one (**I**) of the two independent molecules present in the crystals of cis 1,4-addition product **5**.[19]

Variation of the temperature at which the conjugate addition reactions were quenched with NH_4Cl revealed that trans product **4** is obtained exclusively when the reaction is quenched at below ca. −45 °C but that on warming above this temperature the cis product **5** is increasingly formed. Quenching with Comins' reagent at −78 °C allowed the isolation of trans vinyl triflate **9** in 72% yield, but quenching with this reagent at room temperature resulted in the formation of cis product **5** (40%) along with some labile products that we were unable to isolate (Scheme 5).

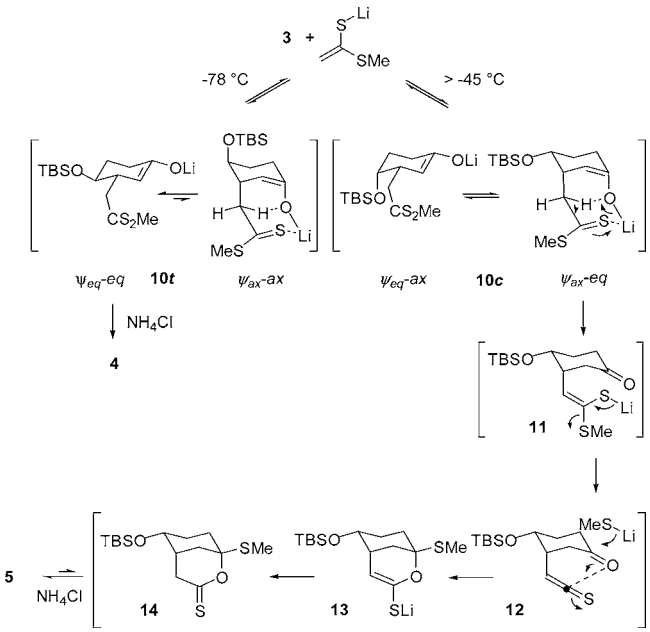
Scheme 5. 1,4-Addition of LMDTA to (±)-4-*O*-TBS-2-cyclohexenone (**3**)[a]—Trapping with Comins' Reagent at −78 °C and Attempted Trapping after Warming to Room Temperature



These results are inconsistent with our original idea that coordination between the lithium of the dithioester enolate and the 4-siloxy group would direct cis addition; the mechanistic situation is clearly more complex. A possible mechanism is outlined below (Scheme 6).

Thus, the trans product **4** is probably formed by direct protonation of the kinetic trans enolate **10t** at low temperature. The cis product **5** may be formed by isomerization of this initially formed trans enolate **10t**, on warming, to the cis enolate **10c** via retro-1,4-addition/re-addition[1] and then irreversible intramolecular ketone to dithioester enolate exchange ($\mathbf{10c}_{\psi ax-eq}$ → **11**). Intramolecular ketone enolate to dithioester enolate exchange has been proposed previously by Metzner who also noted that it occurs at about −45 °C

Scheme 6. Possible Pathway for the Formation of trans and cis Isomers **4** and **5**



following 1,4-addition of dithioester enolates to acyclic enones.[13b] It appears that that in our case the cis enolate conformer $\mathbf{10c}_{\psi ax-eq}$ required for intramolecular exchange to the dithioester **11** is lower in energy by a sufficient amount relative to the corresponding trans enolate conformer $\mathbf{10t}_{\psi ax-ax}$ to allow selective bleeding of the cis enolate from the equilibrium.[21] The subsequent steps could involve thioketene formation (**11** → **12**), methyl thiolate triggered 6-exo-dig cyclization (**12** → **13**), and then isomerization of the tetrahydropyran-2-thione **14** formed on protonation to the 1-methylsulfanyl-2-thiabicyclo[3.3.1]nonan-3-one product **5**.

Irrespective of the mechanistic nuances, the thermally stereodivergent behavior of LMDTA toward 1,4-addition to 4-*O*-TBS-2-cyclohexenone (**3**) provides expedient access to the trans and cis 3,4-functionalized cyclohexanone esters **6t** and **6c** and the corresponding ketolactones **7t** and **7c** from a common precursor. The generality of this stereodivergent behavior with respect to the nature of the C4 substituent is under current investigation in our laboratories.[22]

The rare syn selective addition process is synthetically complementary to that of Danishefsky which provides silyl enol ether products from the same 4-*O*-TBS ether substrates and to that of Liotta which requires the use of 4-hydroxy-2-enones, which in our experience are often labile species.[23] Although using the current method only the anti vinyl triflate **9** could be trapped-out as originally envisaged, the cis addition protocol has proved uniquely suited to our approach to Amaryllidaceae alkaloids as will be reported in due course.

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Supporting Information Available: Experimental procedures and full characterization for compounds **2**−**9** and crystallographic data for compounds **5** and **7t**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Enolates $\mathbf{10c}_{\psi ax-eq}$ and $\mathbf{10t}_{\psi ax-ax}$ differ in the orientation of their respective 4-*O*-TBS substituents (equatorial vs axial); an *O*-TMS substituent has an *A* value of 3.1 kJ mol^{-1}; see *Stereochemistry of Organic Compounds*; Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1994; p 696.

(22) Cyclization to the 1-methylsulfanyl-2-thiabicyclo[3.3.1]nonan-3-one ring system (cf. **5**) on warming does not require the presence of a 4-substituent; using 2-cyclohexenone itself cyclization also ensues (Spivey, A. C.; Martin, L. J. Unpublished).

(23) Spivey, A. C.; Giró Mañas, C.; Mann, I. *Chem. Commun.* **2005**, 4426−4428.