

Double Annulation Route to Fused Bicyclic Compounds with Three Contiguous Quaternary Centers

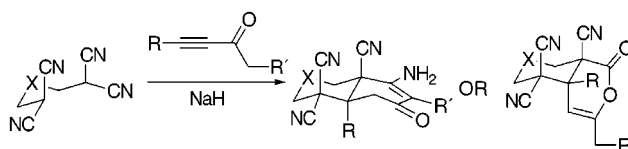
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ABSTRACT



Fused bicyclic and tricyclic compounds featuring two or three new C—C σ bonds, two new rings, two or three new stereocenters, and three new contiguous quaternary centers can be prepared stereoselectively, atom-economically, and in one synthetic operation via a cascade reaction of two nonstereogenic, readily available starting materials: a tethered bis(malononitrile) and an internal alkynone. The course of the “double annulation” changes drastically with the structure of the starting materials, alternately affording *trans*-decalins or *cis*-fused unsaturated lactones.

The efficient and stereoselective introduction of quaternary centers into organic compounds represents a continuing challenge to the synthetic organic chemist.^{1–3} The construction of three contiguous quaternary centers bearing only C substituents is usually seriously impeded by steric encumbrance, and methods for preparing such architectures in one step are few and far between. The few methods reported so far usually use cycloadditions such as the cycloaddition of tetracyanoethylene with terminally disubstituted 1,3-dienes^{4–6} or electron-rich alkenes,^{7,8} the dimerization of tetrasubstituted cyclopentadienones,⁹ and intramolecular [2 + 2] photocycloadditions,^{10,11} although double Michael reactions involving

heavily substituted cyclohexenone enolates and either isopropylidene malononitrile¹² or methyl α -chloro- α -cyclopropylideneacetate¹³ have also been used, and Wender has recently reported a spectacular arene–alkene *meta*-photocycloaddition in which *four* new contiguous quaternary centers are produced in a single step.¹⁴ The fact that to our knowledge only two reactions other than cycloadditions (and only a handful of cycloadditions, for that matter) have previously been reported to make three new contiguous quaternary centers is testament to the difficulty of this transformation. We now report a novel “double annulation” reaction that affords bicyclic products featuring three new σ bonds (two or all three of which are C—C bonds), two new rings, two or three new stereocenters, and three new contiguous quaternary centers from two nonstereogenic, readily available starting materials with excellent stereoselectivity and atom economy. We also report that slight variations in the starting materials produce drastic changes in the course of the double annulation reaction.

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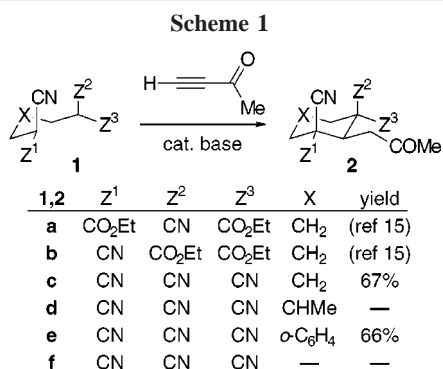
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We recently disclosed that nucleophiles containing two tethered carbon acids (**1**) underwent two sequential Michael reactions to 3-butyne-2-one to give functionalized cycloalkanes (**2**) containing two new quaternary centers (Scheme 1).^{15–17} The reactions proceeded when at least one of the



groups attached to the acidic carbons was a CN group. Compound **2** could then be induced to undergo a Dieckmann reaction to give a *trans*-decalin ($X = \text{CH}_2$) or a *trans*-hydrindan ($X = \text{nothing}$).

Although dicyano diesters **1a** and **1b** smoothly underwent double Michael reactions with the terminal alkyne 3-butyne-2-one, multiple attempts to promote their double Michael reaction with internal alkynes failed to provide any identifiable cyclic products. In our earlier work we had taken advantage of the very low steric bulk of the cyano group,¹⁵ and so we decided to see whether tethered carbon acids containing *only* cyano groups were sufficiently unhindered to react with internal alkynes in a double Michael reaction. The requisite tetranitriles **1c–e** (Scheme 1) were easily prepared in good yield using the protecting group methodology we have reported;¹⁸ that is, (3-pentylidene)malononitrile was alkylated with an α,ω -dibromide, and the product was deblocked by ozonolysis and reflux in acidic EtOH. Unfortunately, we were unable also to prepare tetranitrile **1f** in this way, as it rapidly underwent a Thorpe–Ziegler reaction under the conditions of the deblocking. Both **1c** and **1e** smoothly underwent the double Michael reaction with terminal alkyne 3-butyne-2-one to give monocyclic products **2c** and **2e** in 67% and 66% yields, respectively (Scheme 1).

When **1c** is combined with internal alkyne 4-hexyn-3-one in THF with 1 equiv of NaH, not only does the double Michael reaction proceed smoothly, but it is followed immediately by a Thorpe–Ziegler reaction¹⁹ to give *trans*-decalin **3a** as a single stereoisomer in 48% isolated yield (Scheme 2). The stereochemistry at the ring junction has been

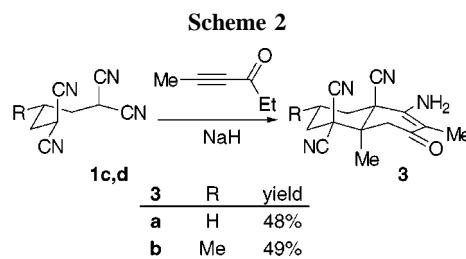
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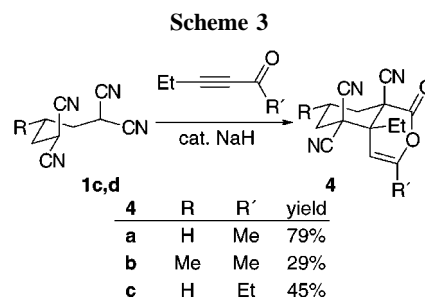
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determined by X-ray crystallography. The reaction of **1d** with 4-hexyn-3-one proceeds similarly to afford *trans*-decalin **3b** as a single stereoisomer in 49% yield.²⁰ These remarkably efficient reactions create *three new C–C σ bonds, two new rings, two or three new stereocenters, and three new contiguous quaternary centers* in one step from two non-stereogenic, readily available starting materials with excellent stereoselectivity and complete atom economy, albeit in moderate yield.²¹

The double annulation takes a very different course when the electrophile has an Et group attached to the triple bond. When **1c** is combined with 3-hexyn-2-one in THF with *catalytic* NaH, the double Michael reaction is followed by attack of the nascent enolate oxygen on a CN group to give *cis*-hexahydroisochromanone **4a** as a single stereoisomer in 79% yield after aqueous acidic workup (Scheme 3). The

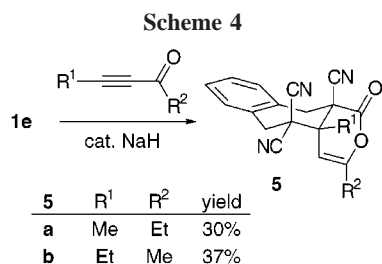


structure of **4a** has been established by X-ray crystallography. The reaction of **1d** with 3-hexyn-2-one proceeds similarly to afford **4b** as a single stereoisomer in 29% yield, and **1c** also reacts stereoselectively with 4-heptyn-3-one to give **4c** in 45% yield.²¹ Either complex mixtures are formed or no reaction occurs when **1c** is combined with the more sterically hindered electrophiles 4-phenyl- and 4-trimethylsilyl-3-butyne-2-one.

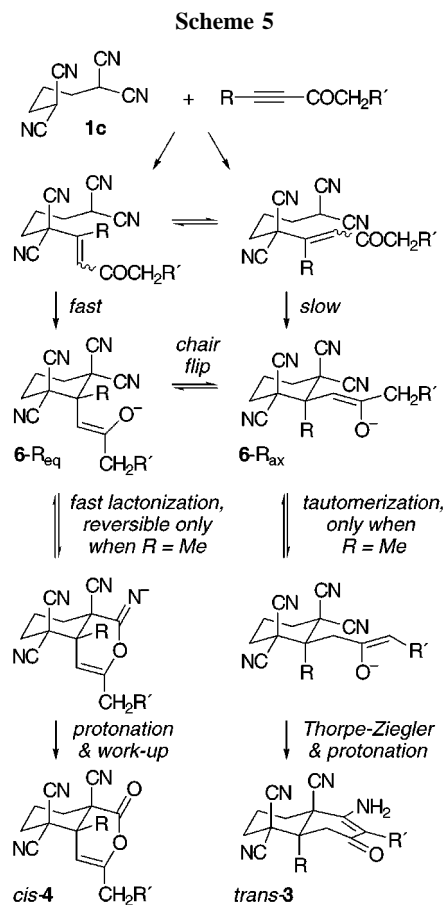
(20) The crystal structure of **3a** reveals N–H \cdots O=C hydrogen bonds (1.99 and 2.15 Å) involving both O lone pairs and both NH hydrogens, and its IR spectrum (KBr) shows two strong, broad absorbances at 3353 and 3195 cm⁻¹. By contrast, the IR spectrum of **3b** shows five strong, sharp absorbances at 3440, 3411, 3350, 3275, and 3242 cm⁻¹, perhaps indicating a lesser degree of hydrogen bonding in this compound. The carbonyl regions of the IR spectra of both of these compounds are also unusual: **3a** shows a strong absorbance at 1551 cm⁻¹ and a weaker one at 1666 cm⁻¹, whereas **3b** shows a strong absorbance at 1548 cm⁻¹ and weaker ones at 1654, 1623, and 1599 cm⁻¹.

(21) Although the yields are low or moderate in some cases, in no case does GC-MS analysis of the crude reaction mixture show any evidence for products with molecular weights identical or close to those of the isolated products.

By contrast with the behavior of **1c,d**, combination of **1e** with either 4-hexyn-3-one or 3-hexyn-2-one affords only the corresponding *cis*-lactones **5a,b** in the indicated yields (Scheme 4). The stereochemistry of the ring junction of **5b** has been determined by X-ray crystallography.^{22,23}



Why does the course of the double annulation change so drastically with small changes in the reagents? A plausible explanation can be formulated upon examination of the nascent double Michael adduct, **6**, that is produced upon combination of **1c** and an internal alkyne (Scheme 5).



Enolate **6** can exist as two interconvertible chair conformers (**6-R_{eq}** and **6-R_{ax}**). The transition states for the formation of **6-R_{eq}** and **6-R_{ax}** should resemble these enolates rather

closely,²⁴ and **6-R_{eq}** is calculated to be about 2–12 kcal/mol lower in energy than **6-R_{ax}** (when R = Et and R' = H; MM2, MOPAC), so the rate of formation of **6-R_{eq}** is probably much greater than that for **6-R_{ax}**.²⁵ When R = Et, the steric compression in **6-R_{eq}** is so great that it lactonizes irreversibly before it has an opportunity to flip to **6-R_{ax}** or to tautomerize, and thus *cis*-**4** is formed exclusively. On the other hand, when R = Me, the smaller steric compression leads to a much slower or a reversible lactonization, an equilibrium is established between **6-R_{eq}**, **6-R_{ax}**, and their tautomeric enolates, and the exclusive formation of *trans*-**3** reflects the lower energy of the TS leading to this thermodynamically preferred isomer (Curtin–Hammett principle). Finally, when R = H, the steric compression is so small that a second cyclization does not occur at all, and **2** is obtained. In support of this hypothesis, when **1d** is combined with 4-hexyn-3-one (R = Me) and the reaction mixture is quenched after 2 h, some isochromanone can be detected in the GC-MS of the crude reaction mixture (*m/z* = 283), but when the reaction mixture is allowed to stir overnight before quenching, only decalin is detected (*m/z* = 282).²⁶ A similar analysis can be carried out with **1e**, except here the greater steric compression attendant upon formation of the seven-membered ring causes the lactonization to occur rapidly and irreversibly even when R = Me.

We must comment on the experimental simplicity of the double annulation reactions. The nucleophile **1** is dissolved in THF at 0 °C, NaH (1.2 equiv for **3**, 0.2 equiv for **4** or **5**) is added, and after 15 min, a solution of the electrophile in THF is added via addition funnel. When the reaction is judged to be complete (TLC or GC, usually a few hours), the reaction mixture is diluted with 1 N HCl, the organic solvent is evaporated, and the aqueous suspension is diluted with EtOH. Less soluble products are isolated in pure form simply by filtration, and more soluble products are isolated by extraction and recrystallization.

In conclusion, we have discovered an efficient, stereoselective route to bi- and tricyclic compounds featuring three new contiguous quaternary centers. Experiments that expand the scope of the double annulation further will be reported in due course.

Acknowledgment. The support of this work by the National Science Foundation (CAREER award to R.B.G., Grant CHE-9733201, and REU program, Grant CHE-

(22) The large *R* value was due to rather large thermal motion, but nothing was found which would have cast doubt on the stereochemistry.

(23) A subsequent X-ray study of this compound revealed the possibility of a second crystal form. Details will be presented in a future publication. Brock, C. P.; Patrick, B. O.; Grossman, R. B.; Skaggs, A. J. Unpublished results.

(24) The Michael reaction in question converts a very stabilized enolate [*pK_a*(conj. acid) ≈ 11] into a moderately stabilized one [*pK_a*(conj. acid) ≈ 20]. Such an elementary step is not expected to be very exothermic, and hence the Hammond postulate suggests that the TS should resemble the product.

(25) The difference in energy between **6-Et_{eq}** and **6-Et_{ax}** seems to be due to dipolar interactions between the axial CN groups and the enolates, not steric interactions.

(26) However, the imide precursors to lactones **4** could not be equilibrated to the corresponding *trans*-decalins, even after the reaction mixtures were allowed to stir with excess base for extended periods of time.

9531406) and the University of Kentucky is gratefully acknowledged. The authors thank Professor Carolyn Brock for preliminary work on the X-ray structure of **4a**.

Supporting Information Available: Experimental procedures and full characterization of **1c–e**, **2c,e**, **3a,b**, **4a–c**,

5a,b, and 2-amino-2-cyclopentene-1,1,3-tricarbonitrile, and X-ray data for **3a**, **4a**, and **5b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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