Double Annulation Route to Highly Substituted and Functionalized Trans-Fused Bicyclic Compounds

Robert B. Grossman,* Melissa A. Varner, and Aaron J. Skaggs

Department of Chemistry, University of Kentucky, Lexington, Kentucky 40506-0055

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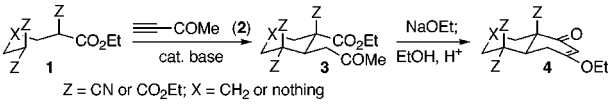
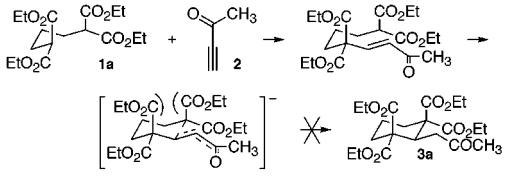
The development of methods for assembling complex compounds from simple ones in as few synthetic steps as possible is a continuing theme in organic synthesis. Methods that allow for the formation of multiple C−C bonds efficiently and stereoselectively are especially valuable.[1,2] We now report a novel method for the synthesis of trans-fused bicyclic compounds, especially *trans*-decalins, that meets these criteria. There is a need for new and efficient methods to prepare highly substituted and functionalized *trans*-decalins, as many biologically active di- and triterpenoids such as neotripterifordin (anti-HIV),[3] longikaurin C (antibacterial),[4] atidine (antiarrhythmic),[5] the gibberellic acids (plant hormones),[6] and azadirachtin (insect antifeedant)[7,8] have highly substituted and functionalized *trans*-decalin or *trans*-hydrindane substructures.

Our method begins with two Michael reactions[9−11] (formally an [n + 1] annulation) of two tethered carbon acids (**1**) and 3-butyn-2-one (**2**) to give a cycloalkylacetone (**3**). "Double Michael reactions" have been used in synthesis before,[12−16] but our method is especially versatile and uses



readily available starting materials.[17] Also, to our knowledge, our version of the double Michael reaction is the first example involving an electrophilic alkyne, rather than two electrophilic alkenes,[9−11] and is the first to create two new quaternary centers[18,19] in a 1,3-relationship. The double Michael reaction is followed by a Dieckmann reaction[20,21] to afford a trans-fused bicyclic compound (**4**), usually a *trans*-decalin. The overall "double annulation" creates three new C−C bonds, two new rings, two new quaternary centers, and two or three new stereocenters in just two synthetic steps. It proceeds stereoselectively, in good yield, and in atom-economical fashion, and the products are highly substituted and functionalized.

Repeated efforts to condense tetraester[22] **1a** with 3-butyn-2-one (**2**) under a variety of conditions led to a complex mixture of many products, none of which was the desired cyclohexane **3a**. Occasionally, the mono-Michael adduct was



isolated in poor yield. We hypothesized that incipient 1,3-diaxial interactions between two ester groups in the transition state for the second, intramolecular Michael addition may have prevented it from taking place and that replacement of two CO_2Et groups with more slender CN groups might facilitate the reaction.[23]

Diethyl 2,6-dicyanopimelate[17,24] (**1b**) does in fact undergo two sequential Michael additions to **2** in CH_2Cl_2 at −78 °C under NaH catalysis to give C_s-symmetric **3b** and C_1-symmetric **3b′** in 52% and 11% yield, respectively (Table 1).[25] The stereochemistry of the *second* Michael addition determines the stereochemistry of the product, and the transition state for this reaction is expected to resemble the product, so it is not surprising that **3b**, the major product, has both CN groups oriented axially.

Two α-cyano ester groups are not required for the double Michael reaction to proceed. Compounds **1c** and **1d**[17] also undergo double Michael addition to **2** to give cycloalkanes **3c** and **3d** in 70% and 69% yields, respectively. Adduct **3c** is obtained in a 99:1 diastereomeric ratio (dr) using *t*-BuOK in CH_2Cl_2 at −78 °C (and only 6:1 dr using NaH in THF at 0 °C); X-ray crystallographic analysis of its Dieckmann product (vide infra) confirms that the CN and acetonyl groups are cis in the major diastereomer, as expected.

The double Michael reaction also proceeds well when the two carbon acids are connected by a two-carbon tether. Diethyl 2,5-dicyanoadipate[17,26] (**1e**) undergoes double Michael addition to **2** to give cyclopentane **3e** as an inseparable mixture of one C_s- and one C_1-symmetric diastereomer in 72% yield. When NaH is used as base in THF at −78 °C to room temperature, the dr immediately after the starting material is consumed is 3:2, but if the reaction mixture is allowed to stir at room temperature, the ratio improves to 8:1. The diastereomers presumably equilibrate by a retro-Michael reaction. The structure of the major diastereomer is assigned as the one in which the acetonyl and CN groups are cis because this isomer is expected to be thermodynamically more stable and because its Dieckmann reaction gives

* To whom correspondence should be addressed. E-mail: rbgros1@pop.uky.edu.

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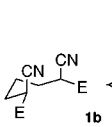
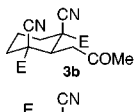
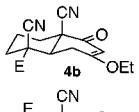
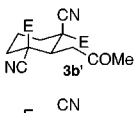
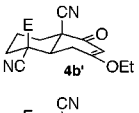
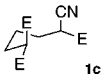
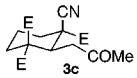
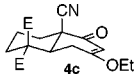
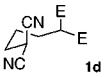
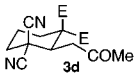
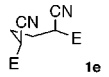
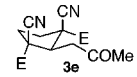
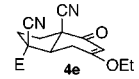
Table 1.[a]

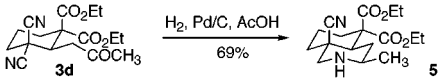
Tethered C acid	Double Michael adduct	dr[b] (base, solvent)	Yield[c]	Dieckmann product	Yield[c]
 **1b**	 **3b**	5:1 (NaH, CH_2Cl_2)	52%	 **4b**	56%
	 **3b'**		11%	 **4b'**	47%
 **1c**	 **3c**	99:1 (*t*-BuOK, CH_2Cl_2)	70%	 **4c**	60%
 **1d**	 **3d**	NA[d] (NaH, THF)	69%	–	–
 **1e**	 **3e**	8:1 (NaH, THF)[e]	72%	 **4e**	20%

[a] E = CO_2Et. [b] Determined by GC−MS of the crude reaction mixture. [c] Isolated yield of >95% pure products. [d] Not applicable. [e] After equilibration.

a *trans*-hydrindane with cis CN groups (vide infra). We have thus far been unable to induce diethyl 2,7-dicyanosuberate (which has a four-carbon tether) to undergo the double Michael reaction.

When **3b**, **3b′**, **3c**, or **3e** is heated in absolute EtOH with an excess of NaOEt, a Dieckmann reaction occurs to form a new, six-membered ring. Treatment of the immediate product with TsOH and EtOH in benzene then affords the corresponding enol ether. In every case, *only a single regio- and diastereoisomer is obtained*. The large coupling constants between the methine H's in **4b**, **4b′**, **4c**, and **4e** and their trans vicinal neighbors (11.7, 12.4, 12.5, and 11.2 Hz, respectively) are consistent only with a trans ring fusion in each of these compounds.[27] Thus, *only the isomers derived from attack of the nascent enolate of **3** on an equatorial CO_2Et group are obtained*. Two inequivalent equatorial CO_2-Et groups are present in **3c**, so two *trans*-decalins could be obtained in principle, but the Dieckmann reaction gives only a single product, **4c**, whose regiochemistry has been unambiguously established by X-ray analysis of a single crystal. Compound **3e** of 5:1 dr gives only a single stereoisomer of **4e** in modest yield after chromatography, but small amounts of three other species (16:1:1:1 ratio) with similar retention times and mass spectra are observed in the GC trace of the crude reaction mixture. The CN groups of isolated **4e** are shown to be cis by X-ray crystallography. The crude GC−MS spectrum suggests that side reactions involving the loss of CO_2Et may account for the low yield. The regiochemistries of enol ether formation in **4** are assigned by analogy to known compounds[28−30] and are confirmed by the X-ray analyses of **4c** and **4e**.

The double Michael adducts are potentially useful starting materials for the synthesis of a variety of other highly functionalized polycyclic compounds. For example, although **3d** suffers from addition of EtOH to the CN groups under the standard Dieckmann conditions,[31] hydrogenation of **3d** over Pd/C in AcOH affords *trans*-perhydroisoquinoline **5** as a single stereoisomer in 69% yield.[32] The selectivity of the reductive amination for the equatorial CN group is noteworthy.



The number of new C−C bonds, rings, and quaternary centers created with our method, its high stereoselectivity, and the ready availability of the requisite starting materials allow our method to be compared favorably to such established routes to trans-fused bicyclic compounds as the Robinson annulation,[33] the intramolecular Diels−Alder reaction,[34] and polyolefin cascade cyclizations.[35] Moreover, our method *immediately* provides quaternary centers at C4 and C10 (diterpenoid numbering) of the decalin ring system, *with all three substituents at these centers functionalized*. The preparation of *trans*-decalins with two or three functionalized substituents at quaternary C4 and C10 has been accomplished only occasionally and usually with poor stereoselectivity,[36,37] Corey's recent synthesis of neotripteriferdin by a cation−π cyclization being a notable exception.[3] The lack of synthetic methods in this area is a serious problem, as numerous di- and triterpenoids that feature highly functionalized *trans*-decalin substructures have interesting biological activity in combination with low toxicity.[3−8]

Experiments to expand the scope of the double annulation reaction further and to apply it to the synthesis of various polyterpenoids are in progress.[38−40]

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Supporting Information Available: Experimental details for the preparation and full characterization of compounds **3**−**5** and diethyl 2,7-dicyanosuberate and X-ray structural information for **4c** and **4e**.

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(27) Compound **4b** can only have a trans ring fusion. If **4b′**, **4c**, or **4e** had a cis ring fusion, the methine H would be equatorial with respect to the B ring in the lower-energy conformer, and a smaller coupling constant to the vicinal trans H would be expected.

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