Synthetic Methods

DOI: 10.1002/anie.200703022

All-Carbon Intramolecular Conjugate Displacement Reactions: An Effective Route to Carbocycles**

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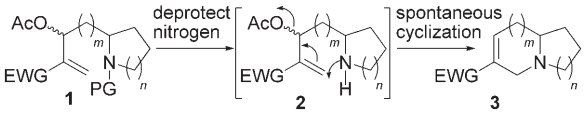
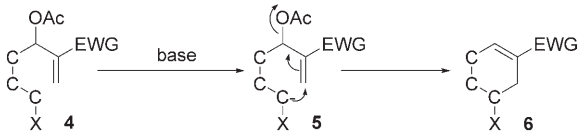
A general method was recently devised in our laboratory for making cyclic amines along the lines shown in Scheme 1.[1,2] The ring closure formally resembles both a conjugate addition



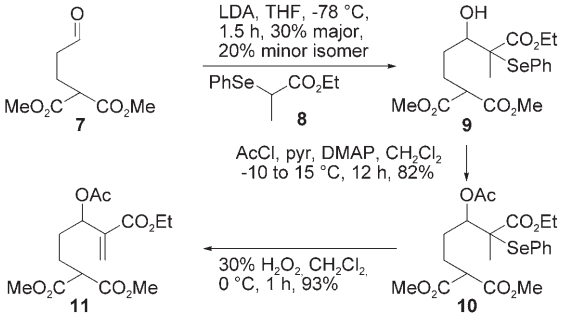
Scheme 1. ICD process for amines. EWG = electron-withdrawing group; PG = protecting group.

and an S_N2' displacement; consequently, the designation intramolecular conjugate displacement (ICD) seems appropriate.[2] An analogous ICD route to carbocycles would clearly be useful, and we report the development of such a method based on the Baylis–Hillman[3] substructural unit **4**, where X is a group that can support an attached nucleophilic carbon atom (Scheme 2).



Scheme 2. The all-carbon ICD process. C = tetravalent carbon atom.

We find that suitable starting materials incorporating the essential features of **4** are easily synthesized by the general route illustrated in Scheme 3 for a particular case.[4,5] In the present study, the electron-withdrawing group on the acceptor double bond was kept constant as an ester, and the other substrates **12**–**20** (Table 1) were also made by the addition of a selenium-stabilized carbanion to an aldehyde (except for **13**) and subsequent selenoxide fragmentation. Treatment of the resulting alkenes with a base, such as DBU,



Scheme 3. Selenium-based route to ICD substrates; LDA = lithium diisopropylamide, DMAP = 4-dimethylaminopyridine.

affords products of the respective ICD reactions (Table 1), usually in over 80% yield.[6]

The reactions shown in entries i–iii of Table 1 (which were monitored by TLC at 5 min intervals) show the dependence of the ICD process on the nature of the leaving group. Acetate **11** reacts more rapidly than the corresponding silyl ether **12**, and in the absence of a leaving group (Table 1, entry iii), cyclization does not take place, at least not under the mild conditions that are effective with the other two substrates. The allylic leaving group and the classical Michael acceptor appear to be mutually reinforcing, and their combination confers a greater degree of reactivity than either feature alone. This phenomenon has been observed in intermolecular reactions with the pivaloate of 2-nitro-2-propen-1-ol.[7]

The example in Table 1, entry iv, for which a secondary amine is required, suggests that an enamine, generated in situ from the aldehyde and the amine, is a suitable nucleophile for the ICD reaction. Initially, we had tried pyrrolidine (11 mol%, PhH, reflux, 18 h, 32%), but the yield is improved using either proline or amine **21** (see Table 1).[8]

Entry vi in Table 1 illustrates an application to bridged systems. With short reaction times (50 min), two products, **16a** and **16b**, were isolated from reaction of **16** (R = Ac or *t*BuCO) with DBU, and we found that **16b** was always the same 7:3 mixture of isomers, irrespective of the stereochemistry at C2 of **16**. Formation of **16b** is reversible, and complete conversion of **16** to **16a** is achieved after a longer reaction time (150 min). With the inorganic base Cs_2CO_3, only **16a** was isolated (greater than 99% yield). When **16b** itself was treated with DBU (room temperature, 12 h), it was converted into **16a** (75%). Presumably, this conversion occurs by a cascade of inter- and intramolecular conjugate displacements: nucleophilic attack at C4 and then attack at C2, both by DBU, and finally the normal ICD process.

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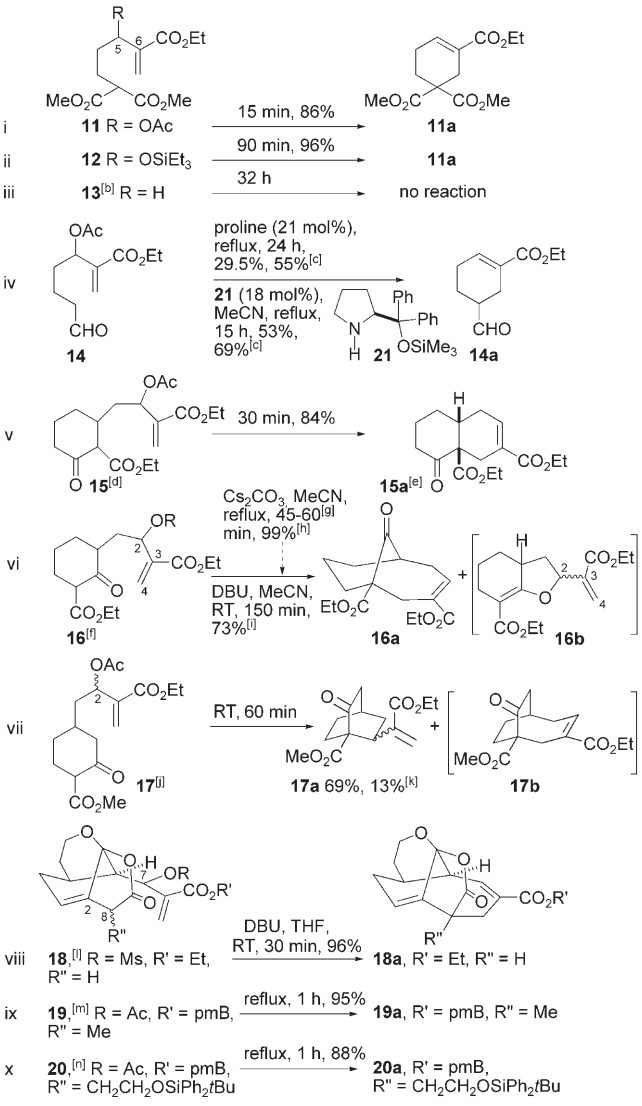
[**] We thank the NSERC for financial support, E. J. L. Stoffman for assistance, and Dr. R. McDonald for the X-ray determination.

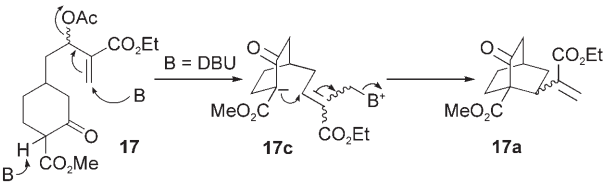
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 1: Intramolecular conjugate displacements.[a]



[a] Unless stated otherwise, reactions were run in MeCN at room temperature, using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base, and yields refer to isolated products. [b] Mixed with the $\Delta^{5,6}$ *E* isomer; $\Delta^{6,7}/\Delta^{5,6} = 3:1$. [c] Corrected for recovered **14**. [d] Mixture of keto and enol tautomers. [e] Tentative stereochemical assignment. [f] Mixture of three isomers (one enol as well as *cis* and *trans* keto forms), R = Ac or *t*BuCO. [g] Depending on which isomer of **16** is used. [h] R = Ac or *t*BuCO, only **16a** isolated. [i] R = *t*BuCO (more polar isomer), only **16a** isolated. [j] Mixture of isomers (including keto and enol tautomers). [k] Major and minor isomers, respectively. [l] Single isomer; Ms = methanesulfonyl, PMB = *p*-methoxybenzyl. [m] Single stereochemistry at C7, both epimers at C8 (85:15). [n] Single stereochemistry at C7, both epimers at C8 (53:47).

Treatment of **17** with base resulted in formation of a six-membered ring and very little, if any, of the expected eight-membered-ring product **17b**. Our working hypothesis for the mechanism (Scheme 4) is based on precedents for consecutive intermolecular conjugate displacements.[9,10] This pathway accounts for the fact that **17**, which is a 1:1 mixture of C2 epimers, gives **17a** as a 1:5 epimeric mixture. A similar mechanism may apply to the formation of **16b** and would



Scheme 4. Proposed mechanism for the formation of **17a**.

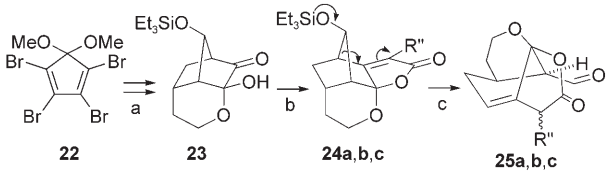
account for the fact that the individual acetates **16** (R = Ac), which differ in stereochemistry only at C2, as well as the corresponding pivaloates (R = *t*BuCO), each give the same ratio (7:3) of isomeric products (**16b**)—an outcome readily accommodated by initial intermolecular conjugate displacement by DBU to remove the asymmetric center at C2.

The considerable power of the ICD reaction is apparent from entries viii–x of Table 1, which illustrate the use of this method to solve a difficult constructional problem. These examples (**18**–**20**) afford the unusual and strained core framework related to the ras farnesyltransferase inhibitors CP-225,917 and CP-263,114.[11]

In the case of mesylate **18**, treatment with DBU at room temperature brought about the desired cyclization (96%), but the ICD reactions of **19** and **20** occurred efficiently only on heating in MeCN in the presence of DBU. The requirement for a higher temperature in these cases, in which C8 carries a non-hydrogen substituent, places a minor restriction on the choice of leaving group at C7. The mesylate corresponding to **19** (Ms instead of Ac) underwent simple 1,2-elimination, but less potent leaving groups, such as acetate or pivaloate, are very satisfactory.

As previously indicated, the starting materials for ICD reactions are readily available by the selenium-based method shown in Scheme 3,[12] and even the complicated structures **18**–**20** are accessible using this method. In these examples, the aldehydes **25a**–**c** (Scheme 5) needed for reaction with **8**, or with the corresponding Pmb ester, were made in just eight steps from 1,1-dimethoxy-2,3,4,5-tetrabromocyclopentadiene (**22**).[12] The two key reactions in this route are the intramolecular Horner–Emmons–Wadsworth olefination (**23**→**24a**–**c**) and the desilylation with fluoride ion, which causes spontaneous strain-assisted fragmentation to release the required aldehydes **25a**–**c**.

The products of all the ICD reactions are themselves classical Michael acceptors and are, therefore, appropriately



Scheme 5. Synthesis of aldehydes **25a**–**c**. For **24** and **25**, R'' = H, Me, $CH_2CH_2OSiPh_2tBu$, for **a**, **b**, and **c**, respectively. Reagents and conditions: a) See the Supporting Information. b) $(EtO)_2P(O)CH(R'')COCl$, Et_3N, then NaH, THF, approximately 60°C, 57% (**24a**), 76% (**24b**), 87% (**24c**). c) Bu_4NF, AcOH, −10 to 0°C, 95% (**25a**), 96% (**25b**), 75% (**25c**).

set up for further useful manipulations. The present method[13] is a metal-free process; hence it offers different opportunities from palladium-catalyzed[14,15] cyclization of allylic acetates and should tolerate the presence of palladium-sensitive groups.

The experiments summarized in Table 1 establish that the ICD process is a general and high-yielding method for constructing a broad range of carbocycles, and the conditions required are mild because of the enhanced reactivity that is characteristic[7] of the simultaneous presence of both a formal Michael acceptor and an allylic leaving group.

Received: July 7, 2007
Revised: July 31, 2007
Published online: October 30, 2007

Keywords: carbocycles · cyclization · Michael addition · S_N2' displacement · synthetic methods

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