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Seebach's Conjunctive Reagent Enables Double Cyclizations

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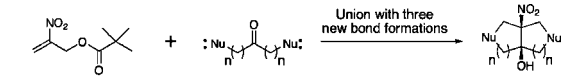
ABSTRACT

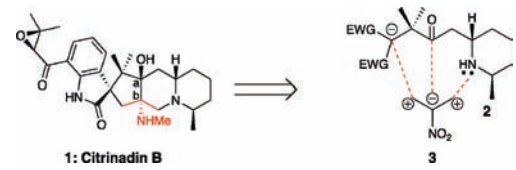


When ketones flanked on both sides by nucleophilic atoms react with Seebach's nitropropenyl pivaloate reagent, direct couplings take place to give two new ring systems and three bonds. *Cis*-ring fusions are observed in unions leading to 5,5-, 5,6-, and 6,6-bicycles. Densely functionalized and rigid frameworks may be rapidly formed by the chemistry described herein.

The general idea outlined in Figure 1 is attractive as a strategy for achieving a double cyclization in the course of an intermolecular union. The impressive synthesis of the adamantane skeleton by Stetter and Thomas[1] offers an excellent example of a bimolecular union with three bond formations and is one of several examples showing the value of conjunctive reagents in syntheses of new rings.[2−6]

Figure 1. Concept for "double cyclization": Nu = nucleophilic atom; X = cation-stabilizing heteroatom; Y = anion-stabilizing functional group.

Scheme 1. Strategy for Synthesizing the Core Architecture of Citrinadin B Featuring the Concept of Double Cyclization



Our laboratory was drawn to the concept shown in Figure 1 as we considered the problem of synthesizing the pentacyclic structure of the scarce, cytotoxic, marine-derived natural product citrinadin B (**1**) (Scheme 1).[7,8] By mentally excising the structural elements highlighted in compound **1** (Scheme 1), we imagined a direct construction of the

(1) Stetter, H.; Thomas, H. G. *Angew. Chem., Int. Ed.* **1967**, *6*, 554.

(2) For ring annulations via the reactions of dimethyl γ-bromomesaconate with enamines of cyclic ketones, see: Nelson, R. P.; Lawton, R. G. *J. Am. Chem. Soc.* **1966**, *88*, 3884.

(3) For a one-pot synthesis of adamantane derivatives via a bimolecular coupling with four bond formations, see: Takagi, R.; Miwa, Y.; Matsumura, S.; Ohkata, K. *J. Org. Chem.* **2005**, *70*, 8587.

(4) For a ring annulation with three bond formations in a synthesis of clusianone, see: Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 12682.

(5) For the use of 2-bromoethyl-3-(trimethylsilylmethyl)buta-1,3-diene in tandem annulations, see: Trost, B. M.; Remuson, R. *Tetrahedron Lett.* **1983**, *24*, 1129.

(6) For uses of 2-nitro-3-pivaloyloxypropene to achieve ring annulations, see: (a) Seebach, D.; Missbach, M.; Calderari, G.; Eberle, M. *J. Am. Chem. Soc.* **1990**, *112*, 7625. (b) Lapierre, J. M.; Gravel, D. *Tetrahedron Lett.* **1991**, *32*, 2319. (c) Eberle, M.; Missbach, M.; Seebach, D. *Org. Synth.* **1993**, *8*, 332.

(7) Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kuwabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430.

(8) The Martin laboratory achieved a concise and stereocontrolled synthesis of the spirooxindole ring system of citrinadin A; see: Pettersson, M.; Knueppel, D.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4623.

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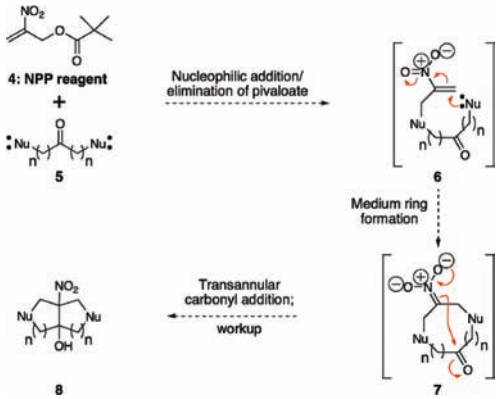
citrinadin architecture by a merger of a functionalized piperidine intermediate of type **2** with a three-carbon, "double annulation" reagent **3** having electrophilic reactivity at the terminal carbons and nucleophilic reactivity at the middle carbon. This would be a pairing by complementary reactivity, and it was our hope that we could identify an appropriate reagent with the characteristics of the hypothetical construct **3**. Implicit in this analysis was the assumption that an attack of a nitro-stabilized anion on the keto group of **2** might be reversible, thus potentially allowing control over the problem of establishing the required relative stereochemistry at carbons a and b, and that the methylamino group of citrinadin B could be elaborated from a nitro group.

In the course of contemplating a suitable laboratory surrogate for a reactive species having the properties of **3**, we encountered the 2-nitro-3-pivaloyloxypropene (NPP) reagent **4** (Scheme 2) introduced by Seebach and Knochel.[6,9]

Scheme 2. Concept for "Double Cyclization"

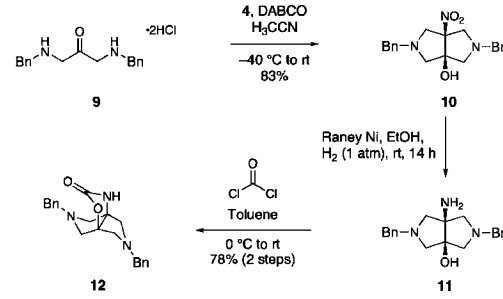


This three-carbon compound was shown to be a reactive conjunctive or "linchpin" reagent[1−6,10] to which new bonds may be readily made to the terminal carbon atoms.

At the outset of our studies, uses of compound **4** as a double-cyclization reagent were not described. We were intrigued by the possibility that structurally rigid and functionalized bicycles of the type shown as **8** (Scheme 2) might arise by simple unions of compound **4** with ketones flanked on both sides by nucleophilic atoms (e.g., **5**). This type of double cyclization could conceivably proceed by a mechanism involving the following sequence of bond formations: (1) an intermolecular conjugate addition reaction with concomitant elimination of pivaloate ion, (2) a ring-forming conjugate addition reaction, and (3) a final transannular carbonyl addition. Our aim was to evaluate the feasibility of this scheme as a strategy for directly generating densely functionalized, bicyclic compounds from acyclic inputs. Rigid, functionalized molecules of type **8** have genuine value in the construction of compound libraries.[11]

Our initial target was a bicyclo[3.3.0]octane framework of type **8** (n = 1; Nu = aminoalkyl) because a double cyclization, if it occurred, would produce a single diastereoisomer due to the well-known thermodynamic bias for a *cis* ring fusion in [3.3.0] bicycles.[12] In our search for reactants of type **5**, we encountered the symmetrical diaminoketone **9**.[13] When the bis-hydrochloride salt of this compound was allowed to react with the NPP reagent **4** under the conditions shown in Scheme 3, *cis*-fused bicyclic nitro alcohol **10** was produced and isolated in 83% yield.[14] The value of Seebach's NPP reagent for the facile production of three new bonds in the course of a simple union was thus demonstrated.

Scheme 3. Direct Synthesis of Bicycle **10** and Chemical Proof of Relative Stereochemistry



DABCO = 1,4-diazabicyclo[2.2.2]octane; Bn = $CH_2C_6H_5$.

Experimental support for the *cis* ring fusion shown in **10** was obtained by the outcome of the following sequence of transformations: (1) a complete reduction of the nitro group in compound **10** with Raney nickel in an atmosphere of hydrogen and (2) conversion of the resulting amino alcohol **11** to carbamate **12** by the action of phosgene. The production of **12** would be possible only if the amino and hydroxyl groups in **11** were situated on the same side of the molecular plane.

(9) Knochel, P.; Seebach, D. *Nouv. J. Chim.* **1981**, *5*, 75. (b) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1981**, *34*, 3223. (c) Seebach, D.; Knochel, P. *Helv. Chim. Acta* **1984**, *67*, 261. (d) Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017. (e) Knochel, P.; Seebach, D. *Tetrahedron Lett.* **1982**, *23*, 3897. (f) Seebach, D.; Calderari, G.; Knochel, P. *Tetrahedron* **1985**, *41*, 4861.

(10) For selected examples of conjunctive reagents (also known as "linchpin" or "multiple coupling" reagents), see: (a) Corey, E. J.; Seebach, D. *Angew. Chem., Int. Ed.* **1965**, *4*, 1075. (b) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231. (c) Trost, B. M.; Vincent, J. E. *J. Am. Chem. Soc.* **1980**, *102*, 5680. (d) Trost, B. M.; Curran, D. P. *J. Am. Chem. Soc.* **1981**, *103*, 7380. (e) Trost, B. M.; Chan, D. M. T. *J. Am. Chem. Soc.* **1979**, *101*, 6429. (f) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed.* **1982**, *21*, 480. (g) For a review of tandem vicinal difunctionalizations, see: Chapdelaine, M. J.; Hulce, M. *Org. React. (N.Y.)* **1990**, *38*, 225. (h) Piers, E.; Yeung, B. W. A.; Fleming, F. F. *Can. J. Chem.* **1993**, *71*, 280. (i) Trost, B. M.; Ghadiri, M. R. *Bull. De la Soc. Chim. Fr.* **1993**, *130* (3), 433. (j) Hoye, T. R.; North, J. T.; Yao, L. J. *J. Am. Chem. Soc.* **1994**, *116*, 2617. (k) Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511. (l) Smith, A. B., III.; Boldi, A. M. *J. Am. Chem. Soc.* **1997**, *119*, 6925. (m) Lipshutz, B. H.; Bulow, G.; Fernandez-Lazaro, F.; Kim, S.-K.; Lowe, R.; Mollard, P.; Stevens, K. L. *J. Am. Chem. Soc.* **1999**, *121*, 11664. (n) Lipshutz, B. H.; Clososki, G. C.; Chrisman, W.; Chung, D. W.; Ball, D. B.; Howell, J. *Org. Lett.* **2005**, *7*, 4561. (o) Smith, A. B., III; Wuest, W. M. *Chem. Commun.* **2008**, 5883. (p) Devarie-Baez, N. O.; Kim, W.-S.; Smith, A. B., III; Xian, M. *Org. Lett.* **2009**, *11*, 1861.

(11) (a) Carell, T.; Wintner, E. A.; Bashir-Hashemi, A.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1994**, *33*, 2059. (b) Carell, T.; Wintner, E. A.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1994**, *33*, 2061.

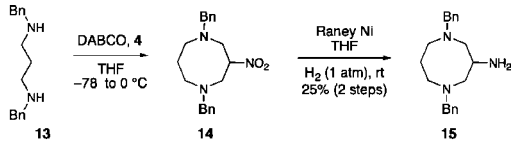
(12) Wiberg, K. B. *Angew. Chem.* **1986**, *98*, 312.

(13) De Michelis, C.; Rocheblave, L.; Priem, G.; Chermann, J. C.; Kraus, J. L. *Bioorg. Med. Chem.* **2000**, *8*, 1253.

(14) Additional bases could also effect unions of compound **9** with NPP reagent **4**. See the Supporting Information for details.

In the course of our studies, we also reacted the known diamine derivative **13**[15] with NPP reagent **4** under the conditions shown in Scheme 4. While there is no opportunity for a double cyclization in this particular instance, the 8-membered ring diazacycle **14** could be isolated, albeit in a low yield, after purification by silica gel chromatography. The production of an 8-membered ring by this direct union provides circumstantial support for the mechanistic scenario outlined in Scheme 2. A reduction of compound **14** with Raney nickel in an atmosphere of hydrogen afforded the more stable triamine derivative **15**.

Scheme 4. Synthesis of an 8-Membered Ring by Bimolecular Union

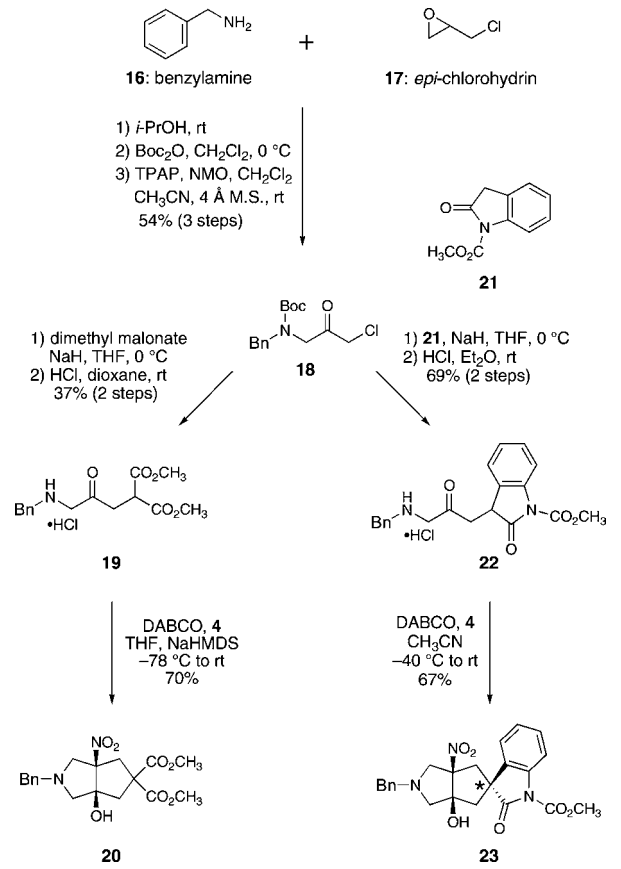


DABCO = 1,4-diazabicyclo[2.2.2]octane; Bn = $CH_2C_6H_5$.

In the wake of the successful double cyclization shown in Scheme 3, we investigated the behavior of carbon-based nucleophiles in this process with a view toward the problem of constructing both 5,5- and citrinadin-like 5,6-fused ring systems. To this end, α-chloro ketone **18** (Scheme 5) was prepared in three straightforward steps from benzylamine (**16**) and *epi*-chlorohydrin (**17**) and subsequently reacted with the stabilized enolate of dimethyl malonate. Cleavage of the Boc carbamate with HCl then afforded hydrochloride salt **19**. The expectation was that the relatively low pK_a's of the ammonium ion and malonate groupings in **19** would permit a base-mediated generation of a species with the chemical character of the hypothetical "double nucleophile" shown in Figure 1; such a species would be unveiled in the presence of Seebach's NPP reagent as a prelude for a union with three new bond formations.

After some experimentation, we found that exposure of a cold (−78 °C) solution of compound **19** and NPP reagent **4** in THF to the combined action of DABCO and sodium hexamethyldisilazide resulted, after warming to room temperature, in the formation of the desired bicyclic system **20**.[16] Compound **20** was isolated in 70% yield, and we did not observe a *trans*-fused diastereoisomer. Not surprisingly, we could also utilize chloromethyl ketone **18** as a building block in a synthesis of the functionalized oxindole **22** (Scheme 5). Our interest in the citrinadin synthesis problem prompted the decision to alkylate the sodium enolate derived from the oxindole derivative **21** with chloromethyl ketone **18**. After the desired carbon−carbon bond formation, the nitrogen-bound Boc group was cleaved with HCl in ether, affording HCl salt **22**. Under the conditions shown, the desired union of compound **22** with the NPP reagent **4** was achieved in 67% yield; this union produced tetracycle **23** as the major component of a 1.9:1 mixture of diastereoisomers, epimeric at the starred carbon atom. Again, the ring fusion stereochemistry of the bicyclo[3.3.0]substructural element was exclusively *cis*.

Scheme 5. Syntheses of Compounds **20** and **23** from a Common Precursor and their Reactions with NPP Reagent **4**[a]



[a] Boc = *tert*-BuOCO; TPAP = tetra-*n*-propylammonium perruthenate; NMO = *N*-methylmorpholine *N*-oxide; DABCO = 1,4-diazabicyclo[2.2.2]octane; NaHMDS = sodium hexamethyldisilazide. Compounds **20** and **23** were produced in racemic form. Two diastereomers of **23**, epimeric at the starred carbon, were isolated in a 1.9:1 ratio favoring the compound shown.

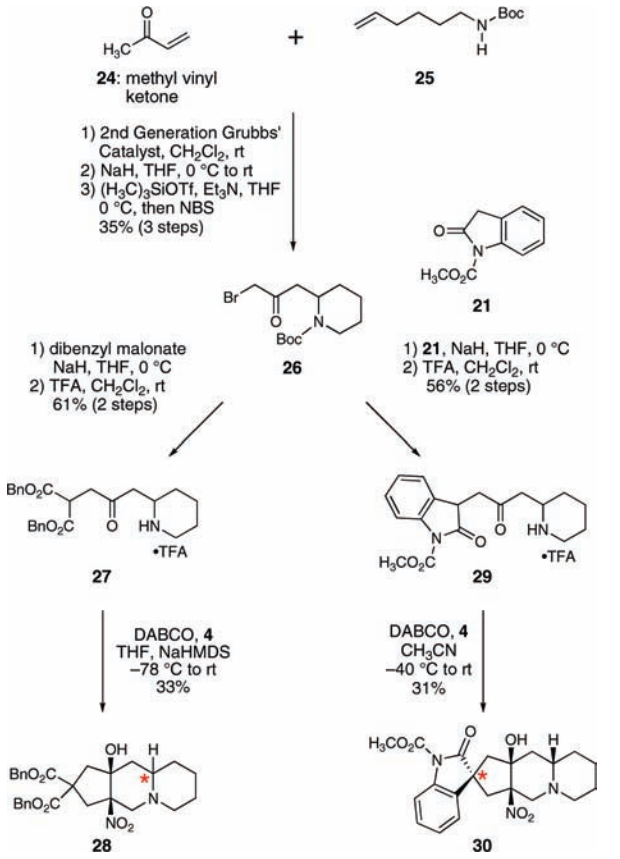
It was also possible to annulate two rings onto a preexisting piperidine framework (Scheme 6). Compounds **28** and **30** were constructed from the same bromomethyl ketone **26**, which was available from methyl vinyl ketone (**24**) and alkenyl carbamate **25**[17] by a three-step sequence featuring an intermolecular olefin cross-metathesis and a ring-forming conjugate addition reaction. As in the syntheses shown in Scheme 6, straightforward enolate alkylations were used to gain access to the multifunctional cyclization substrates **27** and **29**. Both of these compounds reacted with NPP reagent **4** under the conditions indicated to give products **28** and **30**; each product was isolated as 1:1 and 2:1 mixture of separable diastereoisomers, respectively, epimeric at the starred centers.

(15) Teyssot, M.-L.; Fayolle, M.; Philouze, C.; Dupuy, C. *Eur. J. Org. Chem.* **2003**, 54.

(16) The use of a stronger base (NaHMDS) in the generation of compounds **20** and **28** was required to afford the desired double cyclization. In the absence of this added base, compounds of type **6** shown in Scheme 2 are isolated.

(17) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246.

Scheme 6. Syntheses of Compounds **28** and **30** from a Common Precursor and Their Reactions with NPP Reagent **4**[a]

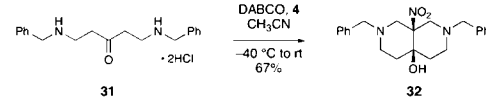


[a] NBS = *N*-bromosuccinimide; TFA = trifluoroacetic acid; DABCO = 1,4-diazabicyclo[2.2.2]octane. Compounds **28** and **30** were produced in racemic form. Two diastereomers of **28**, epimeric at the starred carbon, were isolated in a 1:1 ratio. Two diastereomers of **30**, epimeric at the starred carbon, were isolated in a 2:1 ratio favoring the compound shown.

The constitution of pentacycle **30** is clearly related to that found in citrinadin B. At the outset of our studies, we were cognizant of the possibility that we might change the relative dispositions of the hydroxyl and nitro groups in compounds **28** and **30** by a retro-Henry/Henry process. If feasible, this tactic would afford materials having the type of *trans*-fused ring system found in the citrinadins. In practice, however, compounds **28** and **30** were found to be impervious to the action of basic reagents, and, as of this writing, we have been unable to isomerize the *cis* ring fusions in these compounds to *trans* by a retro-Henry/Henry mechanism.

While the *cis* ring fusions found in compounds **10**, **20**, **23**, **28**, and **30** were anticipated on thermodynamic grounds, we were less certain about the stereochemical outcome of a double cyclization leading to a bicyclo[4.4.0]decanyl nitro alcohol. *Trans*-fused decalins are generally more stable than their *cis*-fused isomers, but we were mindful that an internal hydrogen bond between adjacent hydroxyl and nitro groups could selectively stabilize a *cis*-locked, bicyclic nitro alcohol.[18] When compound **31** was allowed to react with DABCO and NPP reagent **4** in acetonitrile, *cis*-fused, bicyclic nitro alcohol **32** was selectively produced in 67% yield (Scheme 7). The relative stereochemical assignment of

Scheme 7. Synthesis of *Cis*-Fused Bisaminobicyclo[4.4.0]decane



compound **32** was determined by reduction of the nitro group, followed by a subsequent conversion of the resulting amino alcohol to the corresponding cyclic carbamate (see Supporting Information). Thus, in all cases examined so far, we have observed a preference for the formation of *cis*-fused, bicyclic nitro alcohols in reactions of the type outlined in Scheme 2.

The complex, pentacyclic framework of citrinadin B (**1**) inspired the retrosynthetic analysis shown in Scheme 1. The studies described herein demonstrated that Seebach's nitropropene **4**, a compound with a proven utility as a conjunctive reagent in organic synthesis, is also a convenient double annulation reagent. Much of the impact of this chemistry derives from the discovery that new bonds may be made to all three of the carbon atoms of NPP reagent **4** in direct couplings of compounds having an appropriate placement of nucleophilic and electrophilic atoms. Furthermore, these cyclizations demonstrate a strong preference for the *cis*-fused configuration in all systems studied to date. Thus, the NPP reagent is an attractive building block for rapid formations of complex ring systems. Our preliminary studies also suggest that medium-ring formations may be possible in the course of simple unions with the NPP reagent. Further studies are needed to delineate the scope of that aspect of the reactivity of Seebach's NPP reagent.

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Supporting Information Available: Experimental procedures and full characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Support for a bonding interaction between proximate hydroxyl and nitro groups may be found in the significantly lower boiling point of *o*-nitrophenol (216 °C) in relation to *p*-nitrophenol (279 °C). Norwitz, G.; Nataro, N.; Keliher, P. N. *Anal. Chem.* **1986**, *58*, 639.