Evaluation of Diene Hierarchies for Diels–Alder Reactions En Route to Xestocyclamine A: Elaboration of an Ansa Bridge by *B*-Alkyl Suzuki Macrocyclization**

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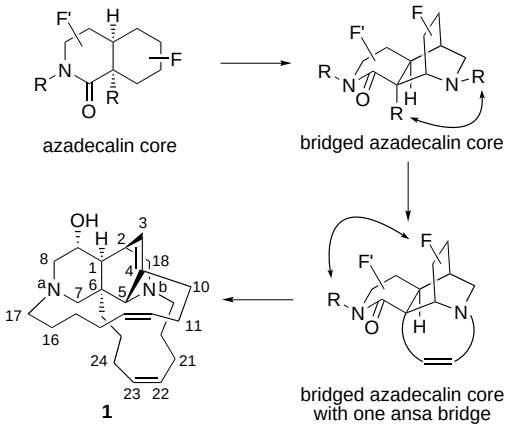
Xestocyclamine A (**1**), a polycyclic alkaloid isolated from *Xestospongia sp.* (a marine sponge collected from the Milne Bay province of Papua, New Guinea)[1] is an inhibitor of PKCβ (PKC = protein kinase C).[2] Compounds that exhibit this type of activity are of biomedical interest. They may be used, in principle, to intervene in a precise manner in the complex chemistry-based communication network that governs the life of a cell through signal transduction.[3] The long-term hope, not yet demonstrated, is that of using specific PKC-directed agents as drugs in the treatment of cancer or other diseases of established mechanism.[4]

In terms of its molecular architecture, xestocyclamine A (**1**) belongs to a broad family of natural products that share a common biogenetic motif.[5] The group includes the manzamines,[6a] the keramiphidins,[6b] the halicyclamines,[6c] the haliclamines,[6d] the ingenamines,[6e] and the ingamines.[6f] From the perspective of the science of synthesis,[7] xestocyclamine presents challenges of some moment. One soon takes note of its interesting 1,4-ethylene-bridged 2,7-diazadecalin matrix, which is further enveloped by two ansa bridges that connect N^a with C4 and N^b with C6 (Scheme 1). Herein, we report on progress directed to reaching xestocyclamine by total synthesis.

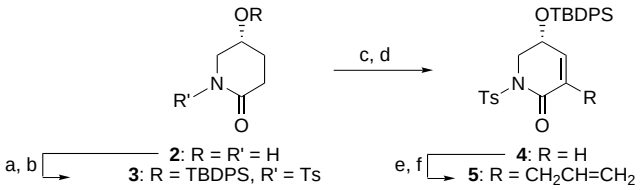
While a variety of options for progressing toward our goal merited consideration, we were particularly disposed toward routes that would make recourse to the *B*-alkyl Suzuki reaction (see below)[8] for the establishment of one or even both ansa bridges. In our judgment, this method can fill an important niche in the establishment of olefinic linkages in complex structures with high stereocontrol. We viewed the xestocylamine project as providing an opportunity to learn more about the reach of the *B*-alkyl Suzuki reaction in organic synthesis.

The matrix of xestocyclamine A consists of an azadecalin moiety with an additional aminomethylene bridge that joins C2 and C5. We first concerned ourselves with building this matrix in a concise way. Once the core was synthesized, we would address the matter of inserting the aminomethylene-based bridge (Scheme 1). Both these subgoals would be attained in a way that allowed the ansa bridges to be stitched together.



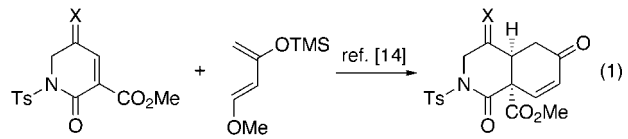
Scheme 1. Strategy for the synthesis of Xestocyclamine A. F, F′ = unspecified functionality.

The synthesis commenced with the conversion of the known enantiomerically pure (*R*)-5-hydroxy-2-oxopiperidine (**2**)[9] into its derivative **3** (Scheme 2). The introduction of a dienophilic double bond into system **3** became the next subgoal. Phenylselenylation of **3** followed by oxidative elimination gave **4**.[10] Precedented iodination[11] followed by Stille coupling[12] allowed the smooth conversion of **4** into **5**. We hoped to establish the *cis*-fused azadecalin matrix with a Diels–Alder reaction by using dienophile **5**.



Scheme 2. Reagents and Conditions : a) TBDPSCl, imidazole, DMF, room temperature, 100%; b) *n*BuLi, THF, 0°C, then TsCl, DMAP, 0°C→RT, 84%; c) LDA, THF, −78°C, then PhSeCl, −50°C, 65%; d) *m*CPBA, CH_2Cl_2, 85%; e) I_2, pyridine, CCl_4, room temperature, 93%; f) 3-iodoprop-1-ene, $Cl_2Pd(PPh_3)_2$, toluene, reflux, 69%. TBDPS = *tert*-butyldiphenylsilyl; DMF = *N*,*N*-dimethylformamide; Ts = *para*-toluenesulfonyl; DMAP = 4-*N*,*N*-dimethylaminopyridine; LDA = lithium diisopropylamide; *m*CPBA = *meta*-chloroperoxybenzoic acid; PMB = *para*-methoxybenzyl.

It is necessary to digress briefly to set our study in its appropriate context. We recall two relevant instances from the literature in which a 3-substituted 5,6-dihydro-α-pyridone functioned as a dienophile in cycloadditions with 1,3-dioxygenated dienes. Thus, dienophile **6**, which has an activating carbomethoxy group at C3 of the dihydropyridone, reacts with diene **7**[13] (which we introduced in 1974) in refluxing benzene to give **9** in moderate yield. Similarly, dienophile **8**, which has an additional γ-siloxy group, also undergoes cycloaddition, albeit in a lower yield [Eq. (1)].[14]



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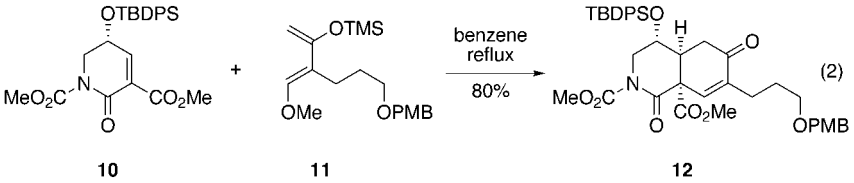
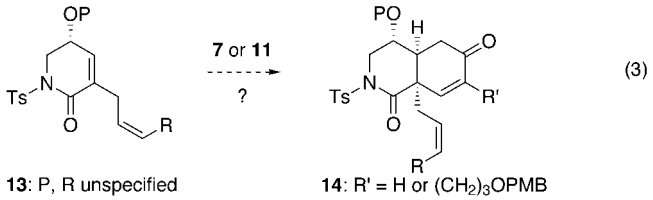
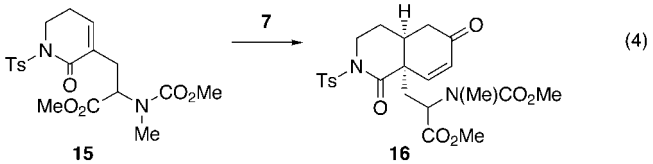
Indeed, an earlier foray of our laboratory directed at xestocylamine, commenced with a Diels–Alder reaction of dienophile **10** with diene **11** to give **12** [Eq. (2)].[15] Although the carbomethoxy group undoubtedly activated the 5,6-dihydropyridone-based dienophile, we were unable to achieve reductive chain extension of the methyl ester grouping (corresponding to C26 of **1**).[15]

Based on these early experiments, we felt that to have a chance to eventually reach **1**, it would be critical to include an appropriate alkenyl group at C3 of the dienophile of the dihydropyridone (i.e. the carbon atom destined to become C6 of **1**). Accordingly, we sought to explore the value of **13** in this context. It was clear that **13** would not be as active as **10** in terms of its dienophilicity.[16] However, a compound such as **14** (P, R = unspecified), which has an angular alkenyl, would be a suitable precursor for our target [Eq. (3)].

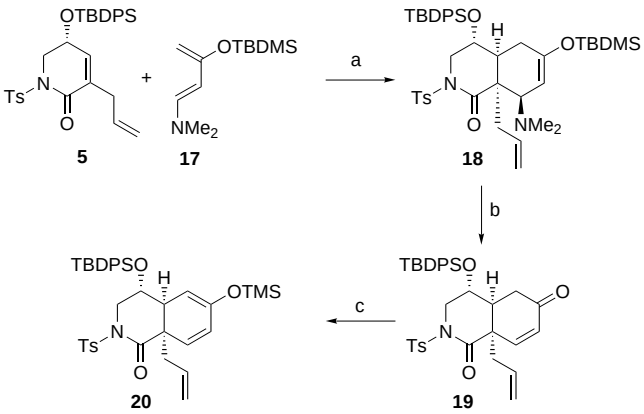




An encouraging precedent that showed that the Diels–Alder cycloaddition (even with a dienophile of type **13**) might be viable for our work was reported by Nakagawa and co-workers, who demonstrated that **15** does, in fact, undergo cycloaddition with diene **7** [Eq. (4)].[17] Although this reaction gave a disappointing yield, we felt that the allyl group in our projected substrate **13** would be less deactivating to Diels–Alder reaction than the branched, highly substituted alanyl derivative at C3 in **15**.



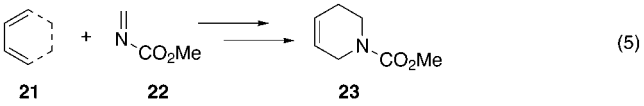
We were therefore quite surprised that **5** did not undergo cycloaddition with either diene **7**[13] or diene **11** under a variety of forcing conditions. We suspect that **5** (**13**) is less reactive than **15** because of the deactivating effect of the highly hindered electron-withdrawing siloxy group at C5.[18] We therefore turned to the use of the Rawal–Kozmin diene (**17**)[19] for cycloaddition with **5** (Scheme 3). Previous



Scheme 3. Reagents and Conditions : a) benzene, reflux, 98%; b) HCl (aq., 2.1N), THF, room temperature, 76%; c) Et_3N, TMSOTf, CH_2Cl_2, 0 °C, 100%. TMSOTf = trimethylsilyl trifluoromethanesulfonate; TBDMS = *tert*-butyldimethylsilyl.

experiments from Rawal and co-workers had shown that **17** is more reactive than **7** in Diels–Alder reactions.[20] Happily, cycloaddition did occur in refluxing benzene to afford exclusively the *endo* adduct **18**, which was treated with acid to afford **19**. Thus, the three critical stereogenic centers (corresponding to C9, C1, and C6 of the target structure) had been established in enantiomerically pure form. Moreover, the diene **20**, projected for the next cycloaddition, could be readily generated.

Our initial plan to advance from **20** involved a variation of the imino Diels–Alder reaction reported by Cava et al. and Krow et al. (**21** + **22** → **23**) [Eq. (5)].[21] Unfortunately, several



attempts at the cycloaddition of **20** with **22** (generated in situ) did not give rise to **24**. A key reaction for the carbon–carbon bond formation at the future C2 involved a method that we introduced in 1976.[22] Reaction of **20** with Eschenmoser's salt (CH_2NMe_2I, **25**)[23] did occur at room temperature (Scheme 4). Attempts to purify the presumed adduct **26** by silica-gel chromatography led to α-methyleneketone **27**. In the long term, it may well be possible to realize the proposed Diels–Alder reaction by fine-tuning the resident groups on the diene and on the azadienophile. However, we decided to proceed via **27**.

For this purpose, the commercially available amino alcohol **28** was converted in a series of straightforward steps into **29**. The *two* desired Michael additions[24] of **29** to **27** (Scheme 5, (1) and (2)) afforded **30** (65%). Unfortunately, but not unexpectedly, the stereoisomeric isoquinuclidone **31** was also formed (25%). Presumably, the formation of **30** and **31** reflects the lack of full α- or β-diastereofacial control in the proton transfer to C2 (with respect to **1**) in the intermolecular (first) Michael addition step, which joins **29** to

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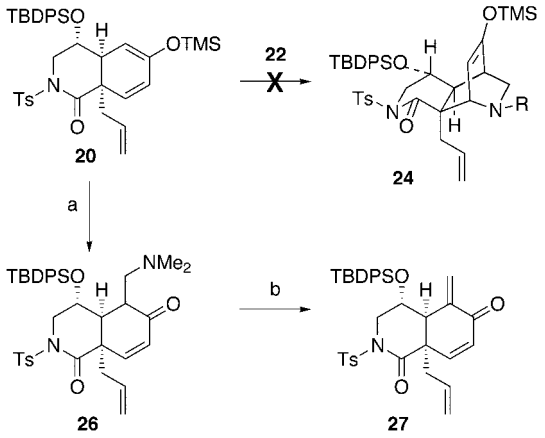
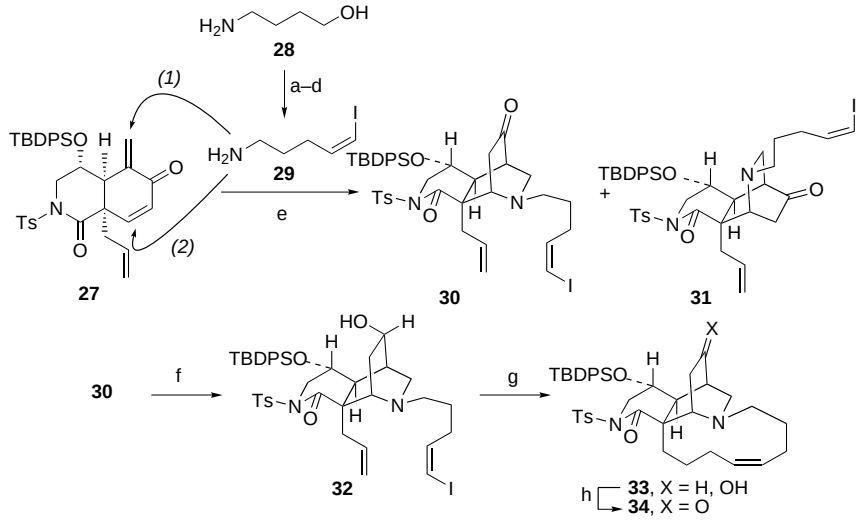


Scheme 4. Reagents and Conditions: a) CH_2NMe_2I (**25**), CH_2Cl_2; b) SiO_2, 85% over 2 steps.

27. Reduction of the keto function of **30** occurred stereospecifically to produce **32**. The stage was now set to test the applicability of the *B*-alkyl Suzuki reaction to close the first ansa bridge. Regiospecific hydroboration of **32** at the terminal vinyl group and subsequent intramolecular coupling led to **33** (60%). The alcohol function was oxidized with Dess–Martin periodinane to provide **34**.[25]

In summary, the appropriate sequencing of three classic reactions, that is, 1) a Diels–Alder cycloaddition (**5**+**17**),[19, 20] 2) an enoxysilane version of the Mannich reaction (**20**→**26**),[22] and 3) a bridging annulation comprised of two Michael additions (**27**+**29**),[26] set the stage for the increasingly powerful *B*-alkyl Suzuki methodology for macrocyclization (**32**→**33**). To reach xestocyclamine A (**1**), another ansa bridge between C4 (with respect to 1) and the nitrogen atom of the A ring must be formed. Moreover, a quality total synthesis will require greater stereochemical control in the formation of **30**. These aims are currently under investigation in our laboratory.



Scheme 5. Reagents and Conditions: a) CbzCl, Et_3N, CH_2Cl_2, 0 °C→RT, 83%; b) ClCOCOCl, DMSO, Et_3N, CH_2Cl_2, −60 °C; c) $Ph_3PCH_2I_2$, NaHMDS, HMPA, THF, −78 °C, 61% over 2 steps, 5.3:1.0; d) TMSI, MeCN, 0 °C, 35%; e) aluminum oxide, weakly acidic, DMSO, room temperature, 5 d, 90%, 2.6:1.0; f) $NaBH_4$, MeOH, 0 °C, 100%; g) 1) 9-BBN, THF, room temperature; 2) H_2O, room temperature; 3) dilution with THF/DMF and slow transfer over Tl_2CO_3, $Pd(dppf)Cl_2$, $AsPh_3$ (syringe pump), 60%; h) DMP, 72%. Cbz = carbobenzyloxy; HMDS = bis(trimethylsilyl)amide; HMPA = hexamethylphosphoramide; DMSO = dimethyl sulfoxide; 9-BBN = 9-borabicyclo[3.3.1]nonane; $Pd(dppf)Cl_2$ = [1,1′-bis(diphenylphosphanyl)ferrocene]dichloropalladium(II); DMP = Dess–Martin periodinane = 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one.

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[1] a) J. Rodríguez, B. M. Peters, L. Kurz, R. C. Schatzman, D. McCarley, L. Lou, P. Crews, *J. Am. Chem. Soc.* **1993**, *115*, 10436–10437; b) revised structure: J. Rodríguez, P. Crews, *Tetrahedron Lett.* **1994**, *35*, 4719–4722.

[2] Y. Nishizuka, *Nature* **1984**, *308*, 693–698.

[3] D. Schechtman, D. Mochly-Rosen, *Oncogene* **2001**, *20*, 6339–6347.

[4] a) J. Hofmann, *Reviews of Physiology, Biochemistry, and Pharmacology* **2001**, *142*, 1–96; b) F. Caponigro, R. C. French, S. B. Kaye, *Anti-Cancer Drugs* **1997**, *8*, 26–33.

[5] J. E. Baldwin, R. C. Whitehead, *Tetrahedron Lett.* **1992**, *33*, 2059–2062.

[6] a) R. Sakai, T. Higa, C. W. Jefford, G. Bernardinelli, *J. Am. Chem. Soc.* **1986**, *108*, 6404–6405; b) J. Kobayashi, M. Tsuda, N. Kawasaki, K. Matsumoto, T. Adachi, *Tetrahedron Lett.* **1994**, *35*, 4383–4386; M. Tsuda, N. Kawasaki, J. Kobayashi, *Tetrahedron Lett.* **1994**, *35*, 4387–4388; M. Tsuda, K. Inaba, N. Kawasaki, K. Honma, J. Kobayashi, *Tetrahedron* **1996**, *52*, 2319–2324; J. Kobayashi, N. Kawasaki, M. Tsuda, *Tetrahedron Lett.* **1996**, *37*, 8203–8204; c) M. Jaspars, V. Pasupathy, P. Crews, *J. Org. Chem.* **1994**, *59*, 3253–3255; B. Harrison, S. Talapatra, E. Lobkovsky, J. Clardy, P. Crews, *Tetrahedron Lett.* **1996**, *37*, 9151–9154; d) N. Fusetani, K. Yasumoro, S. Matsunaga, H. Hirota, *Tetrahedron Lett.* **1989**, *30*, 6891–6894; e) F. Kong, R. J. Andersen, T. M. Allen, *Tetrahedron Lett.* **1994**, *35*, 1643–1646; F. Kong, R. J. Andersen, *Tetrahedron* **1995**, *51*, 2895–2906; f) F. Kong, R. J. Andersen, T. M. Allen, *Tetrahedron* **1994**, *50*, 6137–6144.

[7] For total syntheses of manzamine, see: a) J. D. Winkler, J. M. Axten, *J. Am. Chem. Soc.* **1998**, *120*, 6425–6426; b) M. Nakagawa, *J. Heterocycl. Chem.* **2000**, *37*, 567–581. For other key papers in this area, see: c) J. E. Baldwin, D. A. James, V. Lee, *Tetrahedron Lett.* **2000**, *41*, 733–736; d) J. E. Baldwin, T. D. W. Claridge, A. J. Culshaw, F. A. Heupel, V. Lee, D. R. Spring, R. C. Whitehead, *Chem. Eur. J.* **1999**, *5*, 3154–3161; e) L. Barriault, L. A. Paquette, *Chemtracts: Org. Chem.* **1999**, *12*, 276–281; f) S. F. Martin, J. M. Humphrey, A. Ali, M. C. Hillier, *J. Am. Chem. Soc.* **1999**, *121*, 866–867; g) Y. Morimoto, C. Yokoe, H. Kurihara, T. Kinoshita, *Tetrahedron* **1998**, *54*, 12197–12214; h) E. Magnier, Y. Langlois, *Tetrahedron* **1998**, *54*, 6201–6258; i) Y. Morimoto, C. Yokoe, *Tetrahedron Lett.* **1997**, *38*, 8981–8984; j) L. Gil, X. Baucherel, M. T. Martin, C. Marazano, B. C. Das, *Tetrahedron Lett.* **1995**, *36*, 6231–6234; k) L. Gil, A. Gateau-Olesker, C. Marazano, B. C. Das, *Tetrahedron Lett.* **1995**, *36*, 707–710.

[8] S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676–4701; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544–4568.

[9] C. Herdeis, *Synthesis* **1986**, 232–233.

[10] a) K. B. Sharpless, R. F. Lauer, A. Y. Teranishi, *J. Am. Chem. Soc.* **1973**, *95*, 6137–6139; b) H. J. Reich, I. L. Reich, J. M. Renga, *J. Am. Chem. Soc.* **1973**, *95*, 5813–5815; c) D. L. J. Clive, *J. Chem. Soc. Chem. Commun.* **1973**, 695–696.

[11] C. R. Johnson, J. P. Adams, M. P. Braun, C. B. W. Senanayake, P. M. Wovkulich, M. R. Uskokovic, *Tetrahedron Lett.* **1992**, *33*, 917–918.

[12] a) D. Milstein, J. K. Stille, *J. Am. Chem. Soc.* **1978**, *100*, 3636–3638; b) V. Farina, V. Krishnamurthy, J. S. William, *Org. React.* **1997**, *50*, 1–652.

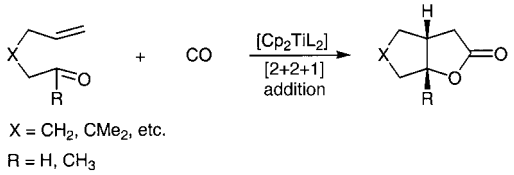
  1433-7851/02/4109-1583 $ 20.00+.50/0

[13] S. Danishefsky, T. Kitahara, *J. Am. Chem. Soc.* **1974**, *96*, 7807 – 7808.
[14] N. Casamitjana, V. López, A. Jorge, J. Bosch, E. Molins, A. Roig, *Tetrahedron* **2000**, *56*, 4027 – 4042; for a recent report of Diels – Alder reactions of dihydropyridinones, see: L. C. Dias, A. M. A. P. Fernandes, J. Zukerman-Schpector, *Synlett* **2002**, 100 – 104, and references therein.
[15] This experiment was conducted by Dr. John J. Cumming—present address: Astra Zeneca Corp., UK.
[16] Although quantitative data for this subject are not readily available, qualitatively, it is certain that the carbomethoxy group enhances the dienophilicity of a double bond much more than that of an allyl group; in fact, it is likely that the allyl group is more deactivating than H.
[17] Y. Torisawa, M. Nakagawa, T. Hosaka, K. Tanabe, Z. Lai, K. Ogata, T. Nakata, T. Oishi, T. Hino, *J. Org. Chem.* **1992**, *57*, 5741 – 5747.
[18] It is not yet clear whether the deactivating effect of the OTBDPS group in **5** is a consequence of its steric hindrance (which curtails access to both the α and β faces of the molecule), or if it arises from an inherent retarding effect of a γ electron-withdrawing group on such cycloadditions; for a discussion on deactivation as a result of such an inductive effect, see: J. G. Allen, S. J. Danishefsky, *J. Am. Chem. Soc.* **2001**, *123*, 351 – 352.
[19] a) S. A. Kozmin, V. H. Rawal, *J. Org. Chem.* **1997**, *62*, 5252 – 5253; b) S. A. Kozmin, J. M. Janey, V. H. Rawal, *J. Org. Chem.* **1999**, *64*, 3039 – 3052; c) S. A. Kozmin, S. He, V. H. Rawal, *Org. Synth.* **2000**, *78*, 152 – 159.
[20] S. A. Kozmin, M. T. Green, V. H. Rawal, *J. Org. Chem.* **1999**, *64*, 8045 – 8047.
[21] a) M. P. Cava, C. K. Wilkins, Jr., D. R. Dalton, K. Bessho, *J. Org. Chem.* **1965**, *30*, 3772 – 3775; b) G. R. Krow, R. Rodebaugh, M. Grippi, G. DeVicaris, C. Hyndman, J. Marakowski, *J. Org. Chem.* **1973**, *38*, 3094 – 3098.
[22] S. Danishefsky, T. Kitahara, R. McKee, P. F. Schuda, *J. Am. Chem. Soc.* **1976**, *98*, 6715 – 6717.
[23] J. Schreiber, H. Maag, N. Hashimoto, A. Eschenmoser, Angew. Chem. **1971**, *83*, 355 – 357; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 330 – 331.
[24] a) For an example of a double Michael reaction on a cross-conjugated dienylketone by using ammonium hydroxide, see: A. Rassat, P. Rey, *Tetrahedron* **1972**, *28*, 741 – 750; b) for a report on a Michael reaction of an *exo* methylene ketone catalyzed by aluminum oxide, see: S. W. Pelletier, A. P. Venkov, J. Finer-Moore, N. V. Mody, *Tetrahedron Lett.* **1980**, *21*, 809 – 812.
[25] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277 – 7287.
[26] To our knowledge, this is the first example of the synthesis of an N-alkyl isoquinuclidone by such a strategy. The scope and limitations remain to be explored.

Synthesis of α-Methylene-γ-butyrolactones: Ru-Catalyzed Cyclocarbonylation of Allenyl Aldehydes and Allenyl Ketones**

Suk-Ku Kang,* Kwang-Jin Kim, and Young-Taek Hong

Recently, Buchwald and co-workers[1] as well as Crowe et al.[2] independently described new titanium-mediated and -catalyzed hetero-Pauson – Khand reactions, which involved the [2 + 2 + 1] cycloaddition of δ-unsaturated ketones and aldehydes with carbon monoxide to form fused bicyclic γ-butyrolactones (Scheme 1). Although titanium catalysis of



Scheme 1. [2 + 2 + 1] Cycloaddition of δ-unsaturated ketones and aldehydes with CO to form fused bicyclic γ-butyrolactones. Ts = toluene-4-sulfonyl.

this process has proven to be efficient, the strength of the early transition metal–oxygen bond makes the catalytic sequence difficult when titanium reagents are used. A solution to this potential problem was provided by Murai and co-workers,[3] who demonstrated that the late transition metal reagent $[Ru_3(CO)_{12}]$ smoothly catalyzes [2 + 2 + 1] cycloadditions of substituted δ-alkynyl aldehydes, with carbon monoxide to form fused α,β-unsaturated γ-butyrolactones.

To the best of our knowledge, late transition metal catalyzed hetero-Pauson – Khand reactions of simple allenyl aldehydes and ketones have not yet been reported. Furthermore, this methodology has not been applied to the synthesis of α-methylene-γ-butyrolactones, a ring system found in numerous, biologically active natural products.[4, 5] Hetero-Pauson – Khand carbonylative cyclizations of δ-allenyl aldehydes and ketones would serve as a direct entry into this family of compounds. We describe herein the preliminary results of an investigation into the latter and demonstrate that ruthenium-catalyzed [2 + 2 + 1] cycloadditions of allenyl aldehydes and ketones with carbon monoxide serve as an efficient and direct route to α-methylene-γ-butyrolactones (Scheme 2).[6–8]

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