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Development of a Stereoselective Co-Mediated Dihydropyran Ring Contraction

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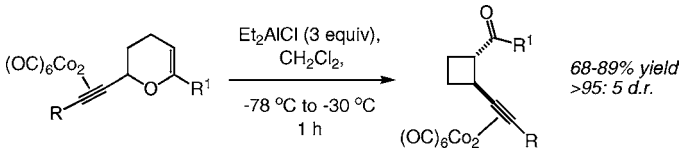
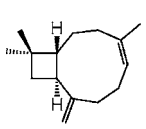
ABSTRACT

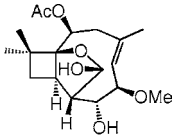


A highly stereoselective approach for the synthesis of trans-1,2-disubstituted cyclobutanes through an Al-promoted cobalt-mediated O→C ring contraction of dihydropyrans is described.

Trans-fused four-membered rings are found in a variety of diverse natural products, such as the sesquiterpenes isocaryophyllene **1**[1] and pestalotiopsin A **2**.[2] Accordingly, the evolution of convergent strategies to heavily functionalized cyclobutane cores has led to numerous methods for their formation.[3] The tactic of generating cyclobutanols via the ring contraction of 2-alkoxy-3,4-dihydro-2*H*-pyrans has been known for more than 25 years[4] yet has rarely been utilized in organic synthesis. More recently, this strategy has been extended to the diastereoselective synthesis of highly functionalized cyclobutanols by the ring contraction of 4-vinylfuranosides mediated by zirconium[5] or samarium iodide.[6] Interestingly, a similar stereoselective strategy to cyclobutanes not bearing a hydroxyl or ether functionality, such as that displayed in **1**, has yet to be developed.



isocaryophyllene **1**



pestalotiopsin A **2**

Studies in our laboratory over the past several years have focused on developing a stereoselective Co-mediated O→C rearrangement and utilizing the protocol in the diastereoselective synthesis of 3-alkynyl cyclic ketones.[7] In this context, we report herein the first example of four-membered ring formation using Nicholas chemistry to form trans-1,2-disubstituted cyclobutanes with excellent stereocontrol.

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[‡] GlaxoSmithKline.

(1) (a) Robertson, J. M; Todd, G. *Chem. Ind.* (*London*) **1953**, *437*; *J. Chem. Soc.* **1955**, 1254. (b) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485.

(2) (a) Pulici, M.; Sugawara, F.; Koshino, H.; Uzawa, J.; Yoshida, S.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 2122. (b) Pulici, M.; Sugawara, F.; Koshino, H.; Okada, G.; Esumi, Y.; Uzawa, J.; Yoshida, S. *Phytochemistry* **1997**, *46*, 313.

(3) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449.

(4) (a) Menicagli, R.; Malanga, C.; Lardicci, L.; Tinucci, L. *Tetrahedron Lett.* **1980**, *21*, 4525. (b) Menicagli, R.; Malanga, C.; Lardicci, L. *J. Org. Chem.* **1982**, *47*, 2288. (c) Snider, B. B.; Phillips, G. B. *J. Org. Chem.* **1983**, *48*, 2789. (d) Malanga, C.; Menicagli, R.; Pecunioso, A.; Lardicci, L. *Gazz. Chim. Ital.* **1991**, *121*, 17.

(5) (a) Ito, H.; Motoki, Y.; Taguchi, T.; Hanzawa, Y. *J. Am. Chem. Soc.* **1993**, *115*, 8835. (b) Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299. (c) Paquette, L. A.; Cunière, N. *Org. Lett.* **2002**, *4*, 1927. (d) Paquette, L. A.; Kim, I. H.; Cunière, N. *Org. Lett.* **2003**, *5*, 221. (e) Paquette, L. A.; Zhang, Y. *Org. Lett.* **2005**, *7*, 511. Paquette, L. A. *J. Organomet. Chem.* **2006**, *691*, 2083.

(6) Aurrecoechea, J. M.; López, B.; Arrate, M. *J. Org. Chem.* **2000**, *65*, 6493.

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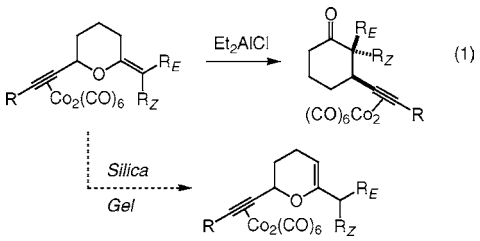
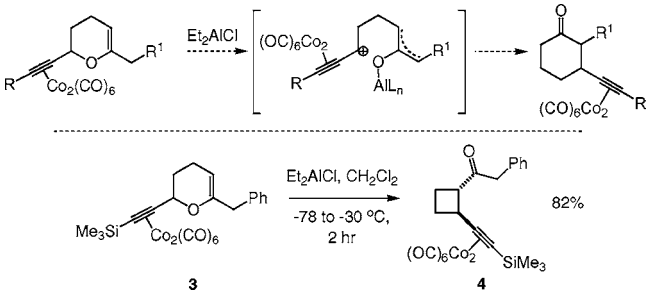
The procedure was discovered inadvertently while investigating the in situ isomerization and cyclization of $Co_2(CO)_6$-complexed 3,4-dihydro-2*H*-pyrans; the isomerization byproduct formed in <5% yield during silica gel chromatography of the parent exocyclic compounds (eq 1). During the course



(1)

of these studies, we noted that when dihydropyran **3** was treated with 3 equiv of commercial grade Et_2AlCl in CH_2Cl_2 at −78 °C and warmed to −30 °C the transient Nicholas carbocation intermediate collapsed smoothly forming *trans*-cyclobutane **4** in good yield and diastereoselectivity (as determined by analysis of the unpurified reaction mixture by 250 MHz ^1H NMR), instead of the anticipated (6-enolendo)-exo-trig[8] cyclized cyclohexanone product (Scheme 1). The stereochemistry of the 1,2-disubstituted

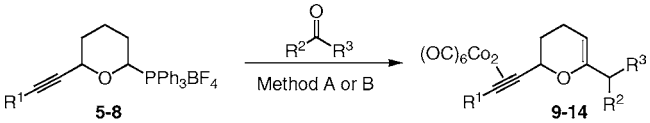
Scheme 1



cyclobutane was assigned on the basis of the ^1H NMR coupling constants embedded within the apparent quartets observed for both cyclobutyl methines ($H_{prop}/H_{\alpha-keto}$; app q, $J \sim 9.0$ Hz) and was consistent with those reported for analogous compounds.[9] On the basis of these unexpected findings, we set out to investigate the potential scope of this novel ring contraction.

First, we examined the synthesis of the requisite dihydropyran rearrangement precursors. On the basis of the above observation that exo to endo enol ether isomerization occurs, albeit in low yield, during silica gel chromatography, we expected that the synthesis of the required pyran substrates could be achieved through isomerization of the parent exocyclic enol ethers by application of an appropriate Brønsted acid. Indeed, we were pleased to find that 5 mol % of pyridinium *para*-toluene sulfonate (PPTS) in CH_2Cl_2 was efficient in effecting this transformation, delivering the products in good yield. Table 1 highlights our results.

Table 1. Synthesis of $Co_2(CO)_6$ Dihydropyran Complexes



entry	R^1	aldehyde/ ketone	method[a]	yield[b]
1	**5**, Ph		A	**9** (33%)
2	**6**, $SiMe_3$		A	**10** (56%)
3	**7**, $CH_2OTBDPS$		A	**11** (52%)
4	**8**, n-Bu		A	**12** (59%)
5	**7**, $CH_2OTBDPS$		A	**13** (47%)
6	**7**, $CH_2OTBDPS$		B	**14** (44%)

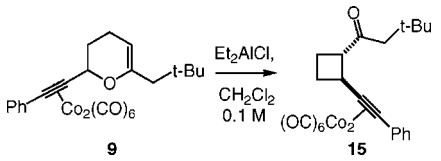
[a] Reagents and conditions. Method A: (a) *n*-BuLi, THF, −78 °C, aldehyde/ketone; (b) $Co_2(CO)_8$, CH_2Cl_2, rt; (c) 5 mol % of PPTS, CH_2Cl_2, rt. Method B: (a) *n*-BuLi, THF, −78 °C, aldehyde/ketone; (b) 5 mol % of PPTS, C_6H_6, 80 °C; (c) $Co_2(CO)_8$, CH_2Cl_2, rt. [b] Yield over three steps.

Wittig olefination between pyranyl phosphonium salts **5**−**8**[7e] and a variety of aldehydes or cyclohexanone, with *n*-butyllithium (THF, −78 °C), afforded the corresponding exocyclic enol ether adducts. The unpurified intermediates[10] were complexed with $Co_2(CO)_8$ (0.1 M in CH_2Cl_2) and then subjected to PPTS (0.05 equiv, 0.1 M in CH_2Cl_2), affording the corresponding dihydropyrans in good yield over the three steps. Isomerization of the alkyl-substituted exocyclic enol ethers with freshly dried PPTS proceeded smoothly to furnish the thermodynamically more stable[11] 3,4-dihydro-2*H*-pyran in 1−3 h in all cases. However, the benzaldehyde-derived substrate (entry 6, Table 1) proved to be more robust to the mild isomerization protocol. Isomerization with 5 mol % of PPTS led only to undesired acyclic products, most likely due to the extra inherent stability of the conjugated aryl enol ether. We were delighted to find that simple reversal of the isomerization and complexation steps in the former sequence and changing the isomerization conditions to 5 mol % of PPTS in benzene (0.1 M, 80 °C, 16 h) yielded the TBDPS-protected 3,4-dihydro-2*H*-pyran **14** in 44% yield from the parent phosphonium salt **7**.

Optimization studies using dihydropyran **9** (Table 2) demonstrated that reactions carried out with 1.5 equiv of Et_2AlCl at either −78 or −30 °C failed to yield any product after >48 h. We were pleased to find that increasing the number of equivalents of Lewis acid to 3.0 led to an increase in yield and a decrease in reaction time, with −30 °C proving

(7) (a) Carbery, D. R.; Reignier, S.; Myatt, J. W.; Miller, N. D.; Harrity, J. P. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 2584. (b) Carbery, D. R.; Miller, N. D.; Harrity, J. P. A. *Chem. Commun.* **2002**, 1546. (c) Carbery, D. R.; Reignier, S.; Miller, N. D.; Adams, H.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4392. (d) Deleuze, A.; Menozzi, C.; Sollogoub, M.; Sinaÿ, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 6680. (e) Meek, S. J.; Pradaux, F.; Carbery, D. R.; Demont, E. H.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 10046.

Table 2. Development of Reaction Conditions

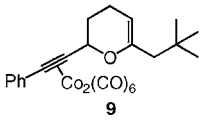
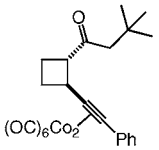
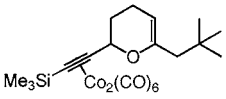
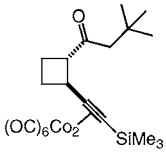
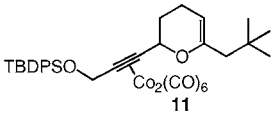
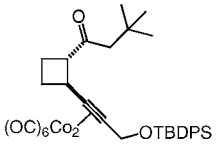
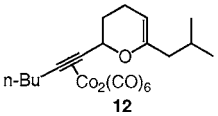
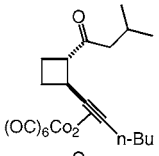
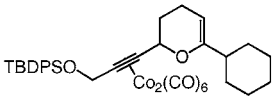
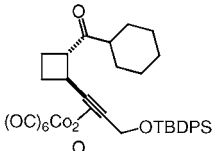
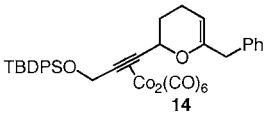
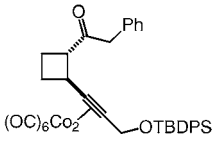


entry	Et_2AlCl	temp/°C	time/h	yield (%)
1	1.5 equiv	−78	>48	–
2	1.5 equiv	−30	>48	–
3	3.0 equiv	−78	5	17
4	3.0 equiv	−78 to −50	5	79
5	3.0 equiv	−78 to −30	2	89

to be the optimum temperature, furnishing the desired cyclobutane **15** in high yield and diastereoselectivity.[12]

Next, we examined the scope of the Co-mediated ring contraction. The results of these studies are presented in Table 3. Accordingly, the rearrangement was found to proceed in good yield and high diastereoselectivity in all cases examined. As shown in entry 1, we established that *trans*-cyclobutane **15**, from unsaturated pyran **9**, can be obtained diastereomerically pure in 89% isolated yield. In addition, recrystallization of **15** from *n*-pentane afforded crystals suitable for X-ray crystallography, allowing unequivocal determination of the relative stereochemistry.[13] The efficiency of the Lewis acid promoted rearrangement was found to be independent of the size of the enol ether appendage and the nature of the alkyne substituent. Notably, cyclohexanone derivative **13**, which carries a more sterically demanding cyclohexyl group attached to the dihydropyran (cf. CH_2R vs CHR_2), cleanly delivered **19** as a single isomer isolated in 68% yield. Finally, rearrangement of benzyl-substituted **14** led to the diastereoselective generation of **20** in 71% yield. Interestingly, the transformations depicted in entries 3, 5, and 6 demonstrate that propargylic silyl ethers are tolerated under the reaction conditions and that Nicholas carbocation formation is regioselective. Furthermore, formation of cyclohexanone products as a result of enolate isomerization (cf. Scheme 1) were not observed in any cases.

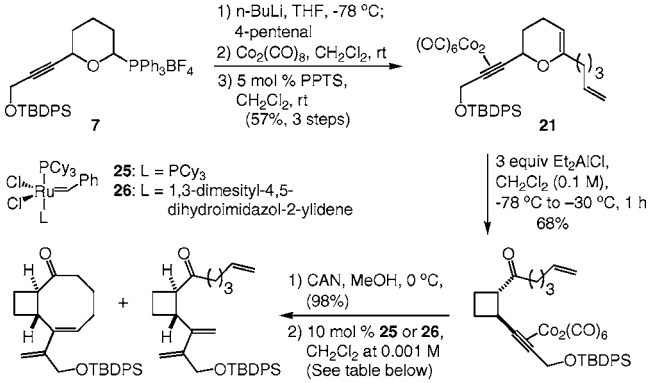
Table 3. Scope of Lewis Acid Promoted Co-Mediated O→C *trans*-Cyclobutane Formation[a]

entry	substrate	cyclobutane[b, c]
1	 **9**	 **15** (89%)
2	 **10**	 **16** (84%)
3	 **11**	 **17** (78%)
4	 **12**	 **18** (86%)
5	 **13**	 **19** (68%)
6	 **14**	 **20** (71%)

[a] Reagents and conditions: 3 equiv of Et_2AlCl, CH_2Cl_2 (0.1 M), −78 to −30 °C, 1−2 h. [b] Products were isolated as a single diastereoisomer as determined by analysis of the unpurified reaction mixture by 250 MHz ^1H NMR. [c] Isolated yield.

Having developed a diastereoselective synthesis of *trans*-cyclobutanes, it was envisaged that the rearrangement described herein could serve as a route toward the bicyclic [*x*.2.0] hydrocarbon framework found in a variety of natural products (e.g., γ-caryophyllene **1**). Accordingly, we opted to construct a model [6.2.0] bicycle via a ring-closing enyne metathesis strategy. Dihydropyran **21** was synthesized by the Wittig reaction of phosphonium salt **7** with commercially available 4-pentenal; transformations analogous to those previously described subsequently furnished complex **21** in 57% yield over three steps (Scheme 2). We were pleased to find that treatment of **21** with 3 equiv of Et_2AlCl (0.1 M in

Scheme 2. Enyne RCM Strategy Toward Bicyclic [*x*.2.0] Hydrocarbon Frameworks



entry	catalyst	atm	temp/ °C	**23**/**24**	yield (%)
1	**25**	$N_{2(g)}$	rt	100/0	27
2	**25**	$CH_2{=}CH_2$	rt	68/32	99
3	**26**	$N_{2(g)}$	reflux	100/0	68
4	**26**	$CH_2{=}CH_2$	rt	56/44	97

CH_2Cl_2, −78 to −30 °C) afforded the *trans*-cyclobutane **22** in 68% isolated yield, notably without detection of Prins-cyclized byproducts.[7b] Elaboration to the bicyclo[6.2.0]-decane ring system commenced by oxidative demetalation, effected by cerium(IV) ammonium nitrate (0.1 M in MeOH) at 0 °C unmasking the alkyne moiety in excellent yield. Subsequent ring-closing enyne metathesis[14] with 10 mol % of Grubbs catalyst **25** or **26** afforded cyclized product **23** in 27% and 68% yields, respectively. Moreover, conducting the Ru-catalyzed ring-closing enyne metathesis under an atmosphere of ethylene[15] resulted in an increase in overall yield. However, triene **24**[16] was isolated along with bicycle **23**.

In summary, we have developed a protocol for the Co-mediated O→C ring contraction of 2,6-substituted 3,4-dihydro-2*H*-pyrans to *trans*-cyclobutanes promoted by Et_2AlCl. The rearrangement process is effective with a range of substrates, particularly dihydropyrans bearing sterically hindered α-branched alkyl groups. Moreover, the variety of methods to form *C*(1)-alkyl and aryl glycals[17] should exhibit the high synthetic utility of the present method. Investigations toward the employment of this technique in target-orientated synthesis are in progress.

Acknowledgment. We are grateful to the EPSRC and GlaxoSmithKline for financial support.

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

OL062329G

(8) Baldwin, J. E.; Lusch, M. J. *Tetrahedron* **1982**, *38*, 2939.

(9) The cis isomer would include one signal with a pseudodiequatorial coupling with $H_{eq}-H_{eq}$ ($J \sim 1.1$ Hz): Raza, G. H.; Bella, J.; Segre, A. L.; Ferrando, A.; Goffredi, G. *Struct. Chem.* **1998**, *9*, 419.

(10) Loss of material is prevented by not purifying the enol ether adduct, which can decompose on silica gel.

(11) Taskinen, E. *Tetrahedron* **1978**, *34*, 433.

(12) The Lewis acid character of dialkylaluminium chlorides has been found to be highly dependent on the reaction stoichiometry: (a) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238. (b) Evans, D. A.; Allison, B. D.; Yang, M. G. *Tetrahedron Lett.* **1999**, *40*, 4457. (c) Castellino, S.; Dwight, W. J. *J. Am. Chem. Soc.* **1993**, *115*, 2986.

(13) Crystallographic data for **15** has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 619257. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax: +44(0)-1223-33603.3 or e-mail: deposit@ccdc.cam.ac.uk).

(14) For a recent review of this area, see: (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317.

(15) (a) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082. (b) Lloyd-Jones, G. C.; Margue, R. G.; de Vries, J. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 7742.

(16) Resubjection of triene **24** to Ru-enyne RCM conditions led only to the recovery of starting material (catalyst **26** has been used in RCM between an alkene and a diene). See: Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 15074.

(17) For recent examples, see: (a) Potuzak, J. S.; Tan, D. S. *Tetrahedron Lett.* **2004**, *45*, 1797. (b) Li, H.; Procko, K.; Martin, S. F. *Tetrahedron Lett.* **2006**, *47*, 3485.