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The Total Synthesis of (−)-7-Deoxyloganin via *N*-Heterocyclic Carbene Catalyzed Rearrangement of α,β-Unsaturated Enol Esters

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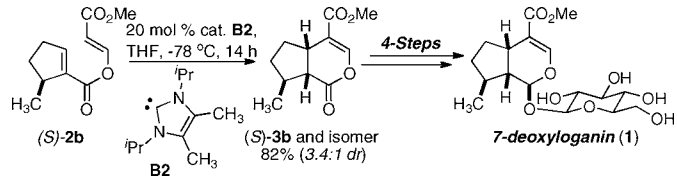
ABSTRACT



The diastereoselective *N*-heterocyclic carbene (NHC) catalyzed rearrangement of α,β-unsaturated enol ester (*S*)-2b has been used to assemble dihydropyranone (*S*)-3b, a material embodying the bicyclic core of the iridoid family of natural products. Elaboration of this intermediate, by chemoselective reduction followed by stereoselective β-glycosylation, has allowed the total synthesis of (−)-7-deoxyloganin (1) to be achieved in four subsequent steps.

Iridoids are an expansive family of monoterpenoid natural products with over 250 members from marine and terrestrial origins.[1] Structurally, the cyclopenta[*c*]pyran core has a cis relationship between H-5 and H-9 in the majority of cases (i.e., **1**), although members lacking this functionality are known. Iridoids have biological relevance, due to their medicinal activity,[1d,e,2] as well as their key role in alkaloid biosynthesis.[3]

Challenges associated with accessing these molecules in a stereocontrolled fashion, along with their biological significance, continue to inspire new approaches to their preparation.[4] While investigating the use of *N*-heterocyclic carbenes (NHCs) as nucleophilic catalysts,[5,6] we uncovered their capacity to rearrange α,β-unsaturated enol esters to form dihydropyranones.[7,8] Using substrates derived from 1,3-diketones, this reaction provided access to materials

(1) (a) El-Naggar, L. J.; Beal, J. L. *J. Nat. Prod.* **1980**, *43*, 649. (b) Boros, C. A.; Stermitz, F. R. *J. Nat. Prod.* **1991**, *54*, 1173. (c) Dinda, B.; Debnath, S.; Harigaya, Y. *Chem. Pharm. Bull.* **2007**, *55*, 159. (d) Dinda, B.; Debnath, S.; Harigaya, Y. *Chem. Pharm. Bull.* **2007**, *55*, 689. (e) Dinda, B.; Debnath, S.; Harigaya, Y. *Chem. Pharm. Bull.* **2009**, *57*, 765.

(2) For a review on bioactive iridoids, see: (a) Tundis, R.; Loizzo, M. R.; Menichini, F.; Statti, G. A.; Menichini, F. *Mini-Rev. Med. Chem.* **2008**, *8*, 399. For resent studies using iridoid scafolds as antiproliferative agents, see: (b) García, C.; León, L. G.; Pungitore, C. R.; Ríos-Luci, C.; Daranas, A. H.; Montero, J. C.; Pandiella, A.; Tonn, C. E.; Martín, V. S.; Padrón, J. M. *Bioorg. Med. Chem.* **2010**, *18*, 2515.

(3) For a useful discussion of iridoids in alkaloid biosynthesis, see: (a) Tietze, L. F. *Angew. Chem., Int. Ed.* **1983**, *22*, 828. and references therein. For recent reviews, see: (b) Oudin, A.; Courtois, M.; Rideau, M.; Clastre, M. *Phytochem. Rev.* **2007**, *6*, 259. (c) Loyola-Vargas, V. M.; Galaz-Avalos, R. M.; Ku-Cauich, R. *Phytochem. Rev.* **2007**, *6*, 307.

(4) For a review on iridoid synthesis, see: (a) Nangia, A.; Prasuna, G.; Rao, P. B. *Tetrahedron* **1997**, *53*, 14507. For recent selected highlights in synthesis, see: (b) Chavez, D. E.; Jacobsen, E. N. *Org. Lett.* **2003**, *5*, 2563. (c) Piccinini, P.; Vidari, G.; Zanoni, G. *J. Am. Chem. Soc.* **2004**, *126*, 5088. (d) Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696. (e) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849. (f) D'Alfonson, A.; Pasi, M.; Porta, A.; Zanoni, G.; Vidari, G. *Org. Lett.* **2010**, *12*, 566. (g) Beckett, J. S.; Beckett, J. D.; Hofferberth, J. E. *Org. Lett.* **2010**, *12*, 1408.

(5) For general reviews on NHC catalysis, see: (a) Enders, D.; Niemeier, O.; Henseler, A. *Chem. Rev.* **2007**, *107*, 5606. (b) Zeitler, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 7506. (c) Johnson, J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1326–1328. For a review on homoenolates, see: (d) Nair, V.; Vellalath, S.; Babu, B. P. *Chem. Soc. Rev.* **2008**, *37*, 2691.

(6) For a review on Lewis base catalysis, see: Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560.

(7) Ryan, S. J.; Candish, L.; Lupton, D. W. *J. Am. Chem. Soc.* **2009**, *131*, 14176.

(8) For a NHC-catalyzed transformation exploiting propargyl aldehydes to access related ring-opened pyranones, see: Kaeobamrung, J.; Mahatthananchai, J.; Zheng, P.; Bode, J. W. *J. Am. Chem. Soc.* **2010**, *132*, 8810.

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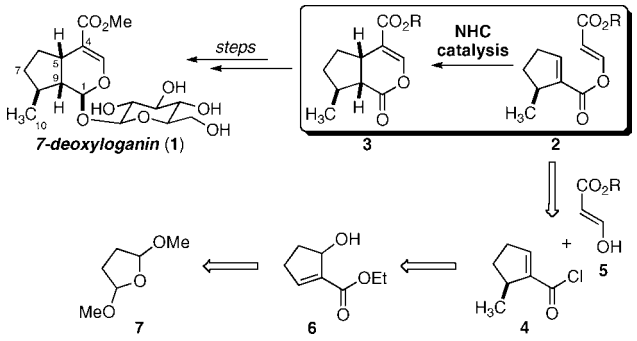
bearing oxygenation as found in various medicinal agents and natural products.[9] Expanding upon these observations and focusing on the iridoid family of natural products, we envisaged the rearrangement of cyclic α,β-unsaturated esters (i.e., **2**) as a method to access bicyclic dihydropyranones (i.e., **3**).[10,11] Herein, we report the outcome of such studies for the preparation of cyclopenta[*c*]pyran **3**, a molecule representing the core of the iridoid family. Subsequent elaboration to (−)-7-deoxyloganin (**1**), a natural product prepared by total synthesis once previously,[12] has also been achieved (Scheme 1).

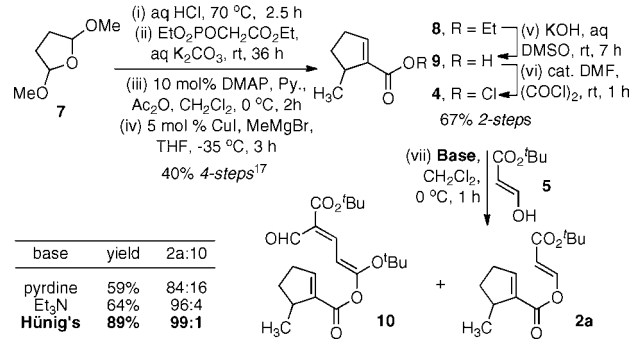
Scheme 1. Synthetic Strategy to (−)-7-Deoxyloganin (**1**)



The central challenge to our synthesis of (−)-7-deoxyloganin (**1**) involved the NHC-catalyzed rearrangement of diene **2**, in the presence of a spectating ester group.[13] In addition to chemoselectivity, this reaction must proceed with substrate-directed stereoselectivity. Finally, elaboration of dihydropyranone **3** to (−)-7-deoxyloganin (**1**) requires a chemo- and stereoselective reduction and a challenging β-glycosylation.[14,15]

Studies commenced with the preparation of hindered *tert*-butyl ester **2a**, a substrate chosen to minimize the possibility of NHC-catalyzed transesterification. Two syntheses of **2a** were investigated; the first involved the RCM of a citronellal derivative[4b] to deliver the aldehydic variant of **8**, which was then oxidized to the acid.[16] This strategy gave the required material. However, for the scalable synthesis of **2a**, it was more practical to start with tetrahydrofuran **7** and use an intercepted Horner−Wadsworth−Emmons reaction to deliver allylic alcohol **6** (Scheme 2).[17] Conversion to ester **8** followed

Scheme 2. Preparation of α,β-Unsaturated Enol Ester **2a**



by hydrolysis then provided acid **9**, which was converted to acid chloride **4**.

Esterification of acid chloride **4**, using *tert*-butyl formyl acetate (**5**)[18] in the presence of pyridine, gave an inseparable mixture of the desired ester **2a**, along with the Knoevenagel adduct **10**. Fortunately, by using Hünig's base, the formation of **10** was eliminated.

Initial attempts to rearrange enol ester **2a** to dihydropyranone **3a** using the NHC derived from diaryl imidazolium **A** met with limited success (Table 1, entries 1 and 2). In related studies, we have found the highly reactive tetramethyl carbene **B1** to be useful with unreactive substrates. In this case, using carbene **B1** at −78 °C in THF gave the desired dihydropyranone **3a**, along with isomeric **3a′**, the former being favored (Table 1, entry 3). Moving to the diisopropyl dimethyl carbene **B2** and decreasing catalyst loading improved the yield and diastereoselectivity (Table 1, entry 4). Conducting the reaction in toluene increased the diastereoselectivity further but decreased the yield (Table 1, entry 5).

(9) For medicinally relevant pyran natural products, see: Prisinzano, T. E. *J. Nat. Prod.* **2009**, *72*, 581.

(10) For other NHC-catalyzed approaches to pyranones, see: (a) He, M.; Struble, J. R.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 8418. (b) He, M.; Uc, G. J.; Bode, J. W. *J. Am. Chem. Soc.* **2006**, *128*, 15088. (c) He, M. H.; Beahm, B. J.; Bode, J. W. *Org. Lett.* **2008**, *10*, 3817. (d) Wang, L.; Thai, K.; Gravel, M. *Org. Lett.* **2009**, *11*, 891. (e) Li, G.-Q.; Dai, L.-X.; You, S.-L. *Org. Lett.* **2009**, *11*, 1623.

(11) For selected transition-metal-based approaches to pyranones, see: (a) Itoh, K.; Hasegawa, M.; Tanaka, J.; Kanemasa, S. *Org. Lett.* **2005**, *7*, 979. (b) Evans, D. A.; Thomson, R. J.; Francisco, F. *J. Am. Chem. Soc.* **2005**, *127*, 10816. For organocatalytic approaches not using NHCs, see: (c) Tozawa, T.; Nagao, H.; Yamane, Y.; Mukaiyama, T. *Chem. Asian J.* **2007**, *2*, 123. (d) Calter, M. A.; Wang, J. *Org. Lett.* **2009**, *11*, 2205.

(12) Tietze, L. F.; Denzer, H.; Holdgrün, X.; Neumann, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *12*, 1295.

(13) For applications of NHCs in transesterification catalysis, see: (a) Grasa, G. A.; Singh, R.; Nolan, S. P. *Synthesis* **2004**, 971. (b) Grasa, G. A.; Kissling, R. M.; Nolan, S. P. *Org. Lett.* **2002**, *4*, 3583. (c) Nyce, G. W.; Lamboy, J. A.; Connor, E. F.; Waymouth, R. M.; Hedrick, J. L. *Org. Lett.* **2002**, *4*, 3587. (d) Nyce, G. W.; Glauser, T.; Connor, E. F.; Möck, A.; Waymouth, R. M.; Hedrick, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 3046. (e) Suzuki, Y.; Yamauchi, K.; Muramatsu, K.; Sato, M. *Chem. Commun.* **2004**, 2770. (f) Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005**, *7*, 1347. NHC-catalyzed transesterification with amino alcohols and mechanistic comments: (g) Movassaghi, M.; Schmidt, M. A. *Org. Lett.* **2005**, *7*, 2453. (h) Schmidt, M. A.; Müller, P.; Movassaghi, M. *Tetrahedron Lett.* **2008**, *49*, 4316. For a detailed mechanistic investigation, see: (i) Pignataro, L.; Papalia, T.; Slawin, A. M. Z.; Goldup, S. M. *Org. Lett.* **2009**, *11*, 1643. For computational studies, see: (j) Lai, C.-H.; Lee, H. M.; Hu, C.-H. *Tetrahedron Lett.* **2005**, *46*, 6265.

(14) In Büchi's seminal contributions, glycosylation was achieved in very low yield: Büchi, G.; Carlson, J. A.; Powell, J. E., Jr.; Tietze, L. F. *J. Am. Chem. Soc.* **1973**, *95*, 540, and references cited therein.

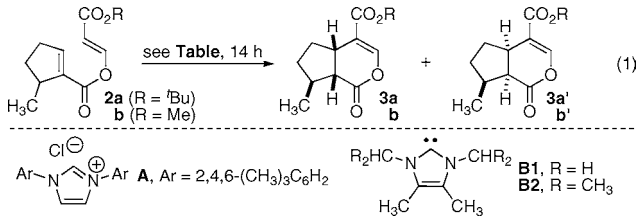
(15) For glycosylation with TMSOTf, see: (a) Tietze, L.-F.; Fischer, R. *Tetrahedron Lett.* **1981**, *22*, 3239. (b) Tietze, L.-F.; Fischer, R. *Angew. Chem., Int. Ed.* **1983**, *22*, 888, and references cited therein.

(16) Bal, B. S.; Childers, W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(17) (a) Graff, M.; Al Dilaimi, A.; Seguineau, P.; Rambaud, M.; Villiéras, J. *Tetrahedron Lett.* **1986**, *27*, 1577. (b) Villiéras, J.; Rambaud, M.; Graff, M. *Synth. Commun.* **1986**, *16*, 149.

(18) (a) Bihmayer, G. A.; Derkosch, D. J.; Polansky, O. E. *Monatsh. Chem.* **1967**, *98*, 564. (b) Sato, M.; Yoneda, N.; Katagiri, N.; Watanabe, H.; Kaneko, C. *Synthesis* **1986**, 672.

Table 1. Selected Optimization of NHC Rearrangement of **2a** or **2b**



entry	SM	mol % catalyst	temp (°C)/solvent	yield of **3**[a] (%)/dr[b]
1	**2a** (R = ^{t}Bu)	10% **A**[c]	rt/toluene	
2	**2a** (R = ^{t}Bu)	10% **A**[c]	−10/toluene	5
3	**2a** (R = ^{t}Bu)	40% **B1**[d]	−78 → rt/THF	40 (2:1)
4	**2a** (R = ^{t}Bu)	30% **B2**[d]	−78 → rt/THF	74 (3:1)
5	**2a** (R = ^{t}Bu)	30% **B2**[d]	−78 → rt/toluene	38 (4.4:1)
6	**2b** (R = Me)	20% **B2**[d]	−78 → rt/THF	82 (3.4:1)

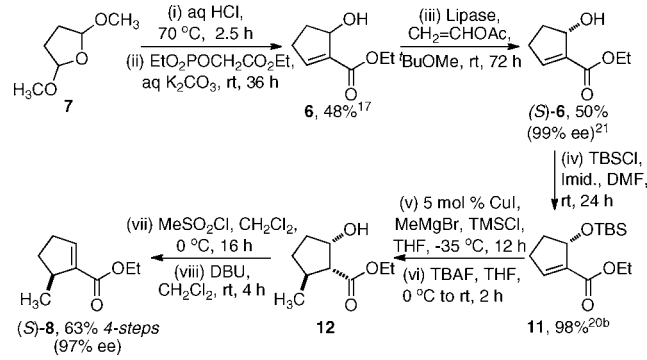
[a] Combined isolated yield. [b] Diastereomeric ratio from analysis of ^{1}H NMR of the unpurified residue. [c] Carbene generated with 10 mol % KO^{t}Bu. [d] Carbene from the reduction of the thiourea and isolated.

While the original strategy targeted *tert*-butyl ester **2a**, it was decided to attempt the rearrangement with methyl ester **2b**, as required for the natural product.[19] This substrate, with 20 mol % of carbene **B2**, provided the dihydropyranones **3b** and **3b′** in a 3.4:1 ratio and 82% isolated yield (Table 1, entry 6). Further optimization, through the use of chiral carbenes, alternate solvents, and temperatures, met with limited success. Therefore, we settled upon the previous conditions.

With proof of principle for the key step, we required access to enantioenriched (*S*)-**2b** to complete the total synthesis. The racemic variant of TBS alcohol **11** has been converted to cyclopentane **12** by stereocontroled anti addition of the methyl group.[20] Thus, access to enantioenriched **11** should, via **12**, provide (*S*)-**8**. To prepare cyclopentene **11**, lipase resolution of the racemic alcohol **6** was undertaken providing (*S*)-**6** in, as reported,[21] 50% yield and 99% ee (Scheme 3). Methylation[20] and deprotection then gave alcohol **12**. Mesylation of **12** and subsequent elimination delivered (*S*)-**8** with good stereochemical integrity.

With access to enantioenriched (*S*)-**8**, and exploiting our previously introduced strategy (Scheme 2), the acid chloride (*S*)-**4** was prepared and then acylated to provide (*S*)-**2a**. Conversion of the *tert*-butyl ester to the methyl ester was achieved, in two steps and 78% overall yield, by TFA deprotection and methylation using TMS-diazomethane (Scheme 4). This strategy was pursued as preparation and

Scheme 3. Preparation of Enantioenriched Cyclopentene (*S*)-**8**[a]



[a] Enantiomeric excess by chiral HPLC, Daicel OD-H.

purification of the more desirable methyl formyl acetate proved difficult,[22] while acylation of (*S*)-**4** with impure formyl acetate gave products contaminated with the Knoevenagel adduct. NHC-catalyzed rearrangement of **2b** (R = Me), as in Table 1, then gave dihydropyranone (*S*)-**3b** in 63% isolated yield and without any loss of stereochemical purity.

Having constructed cyclopenta[*c*]pyranone (*S*)-**3b**, it remained to reduce the lactone and introduce the glycoside. The chemoselective reduction of related iridoid lactones has been achieved.[23] However, over-reduction has also been observed.[24] In our hands, reduction with $NaBH_4$, followed by acetylation, gave lactol acetate **13** in 41% isolated yield over two steps.

At this stage, our studies intercepted those of Tietze.[12] Unfortunately, spectral data was not reported for acetate **13**, making completion of the total synthesis a requirement to allow comparison with the literature and to update the data associated with the natural product.[25,26]

The stereoselective β-glycosylation of iridoid agylcons is a challenge using traditional methods.[14] However, Tietze has developed useful conditions for this reaction using catalytic TMSOTf.[15] Exploiting these conditions, in acetonitrile[15a] rather than liquid SO_2,[15b] permitted the stereoselective conversion of acetate **13** into β-glycoside **14**.[27] We found that partial purification of **14**, followed by deprotection and further purification, gave glycoside **1** in yields consistent with the literature. Comparison of the ^{1}H and ^{13}C NMR data derived from **1** to that reported[25,26] provided confirmation of the structure as (−)-7-deoxyloganin (**1**).

In summary, a total synthesis of (−)-7-deoxyloganin (**1**) has been achieved in 18 steps from **7** and 0.8% overall yield.

(19) While the mechanism of NHC catalyzed tranesterification is not settled, base mediated alcohol activation appears most likely, ref 13g−j. This cannot operate under our reaction conditions; hence, the type of ester should be irrelevant.

(20) (a) Dambrin, V.; Villiéras, M.; Moreau, C.; Amri, H.; Toupet, L.; Villiéras, J. *Tetrahedron Lett.* **1996**, *37*, 6323. (b) Dambrin, V.; Villiéras, M.; Janvier, P.; Toupet, L.; Amri, H.; Leberton, J.; Villiéras, J. *Tetrahedron* **2001**, *57*, 2155.

(21) Yamane, T.; Takahashi, M.; Ogasawara, K. *Synthesis* **1995**, 444.

(22) Methyl formyl acetate is prone to oligomerization, as reported previously: Dinh, M.-T.; Bouzbouz, S.; Péglion, J.-L.; Cossy, J. *Tetrahedron* **2004**, *64*, 5703.

(23) Brown, R. T.; Ford, M. J. *Tetrahedron Lett.* **1990**, *31*, 2033, and references therein.

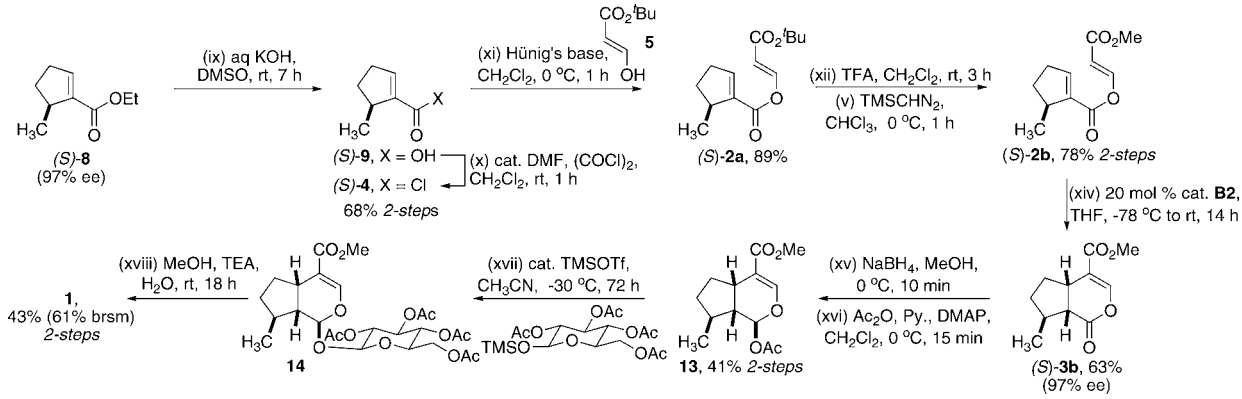
(24) Balsevich, J.; Bishop, G. *Heterocycles* **1989**, *29*, 921.

(25) Kocsis, A.; Szabó, L. F.; Podányi, B. *J. Nat. Prod.* **1993**, *56*, 1486.

(26) Damtoft, S.; Jensen, S. R.; Nielsen, B. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1943.

(27) For the application of the reaction conditions introduced in ref 15, see ref 4d.

Scheme 4. Synthesis of (−)-7-Deoxyloganin (**1**)



The key transformation exploits a substrate-directed NHC-catalyzed rearrangement to generate cyclopenta[*c*]pyranone (*S*)-**3b**, the bicyclic core of the iridoid family of natural products. The reaction was achieved in good yield and with stereocontrol through the application of the underutilized NHC **B2**. Elaboration of (*S*)-**3b** by chemoselective reduction and glycosylation of lactol acetate **13** then completes the synthesis.

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Supporting Information Available: Experimental procedures, characterization of all new compounds, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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