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The domino intramolecular Diels–Alder approach to 16-oxasteroids†

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This communication describes the use of the zipper mode domino IMDA strategy for the one step construction of enantiomerically pure steroid-type frameworks.

The most powerful strategies for complex organic molecule synthesis involve short, convergent routes to enantiomerically pure materials.[1] Domino sequences are useful for achieving brevity in synthesis since they combine several bond-forming events in one process that can be carried out under identical or nearly identical reaction conditions.[2] Domino sequences involving cycloaddition reactions are particularly effective processes for the rapid elaboration of complex polycyclic systems, since each cycloaddition event generates a new ring and two new covalent bonds.[3] We recently reported that simple achiral, acyclic precursors give tetracarbocyclic products of the D-homosteroid class through a novel Lewis acid-promoted domino sequence of two intramolecular Diels–Alder (IMDA) reactions.[4] In this communication we show that this "zipper mode" domino IMDA strategy allows the rapid construction of steroid-type frameworks. In addition, we demonstrate that relative product stereochemistry can be controlled by existing stereochemistry in the precursor; specifically, a substituent at the usual point of attachment of the steroid side chain. We also show that both enantiomeric forms of this tetracyclic framework are accessible in short sequences from D-glucose and D-galactose, the most inexpensive of starting materials.

Enantiomerically pure domino Diels–Alder precursor **7** was prepared from glucose as shown in Scheme 1.

Wittig reaction between enal **1**[5] and the semistabilised ylide derived from 2,4-pentadienyl triphenyl phosphonium bromide[6] gave the conjugated tetraene as a mixture of geometrical isomers from which the *E*,*E*,*E*-isomer **2** was obtained in excellent yield after iodine-catalysed equilibration and HPLC purification. Hydrolysis of the acetates gave the unstable tetraene triol **3**, which underwent selective acetal formation in high yield.[7] The bis-dienophile acid **6** was prepared in three steps from known alkyne-acetal **5**.[8] The carboxylic acid residue was introduced first. Deprotection of the acetal functionality then liberated the aldehyde, which underwent a highly *E*-selective Wittig reaction with $MeO_2C–CH=PPh_3$ to furnish bis-dienophile acid **6**. This compound was condensed with bis-diene alcohol **4** to give the domino IMDA precursor **7** in good yield.

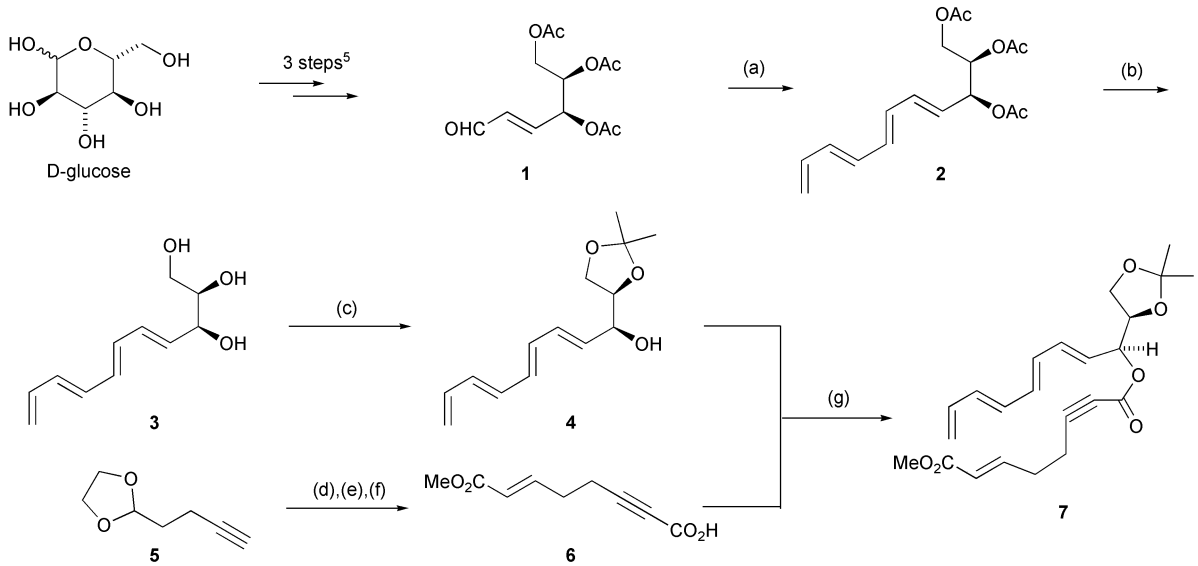
Gratifyingly, thermolysis of precursor **7** in refluxing chlorobenzene for 45 minutes gave a very clean double IMDA reaction[9] that furnished only two of the eight possible stereoisomeric tetracyclic products, **8** and **9** (Scheme 2).

Product stereochemistries were assigned on the basis of NMR experiments and single crystal X-ray analyses.§

As expected, the first IMDA reaction between the internal diene and the alkynic dienophile proceeds with high π-diastereofacial selectivity to give the C13,C17-*anti*-stereochemistry.[10] The second IMDA reaction gives products bearing the 5,10-*cis*;9,10-*syn*-stereochemistry **8** and the 5,10-*trans*;9,10-*anti*-stereochemistry **9** in a *ca*. 3 : 2 ratio. The

† Electronic supplementary information (ESI) available: experimental procedures, product characterisation data and ^1H NMR spectra for **8**, **9**, **11** and **12**; ORTEP diagrams for **9** and **11**. See http://www.rsc.org/suppdata/cc/b3/b303362g/

‡ Author to whom correspondence should be addressed regarding crystal structures.



Scheme 1 From glucose to the domino IMDA precursor. *Reagents and conditions*: (a) 1. CH_2=CH–CH=CH–CH_2–PPh_3Br (1.05 equiv.), *n*-BuLi (1.00 equiv.), THF, Ar, −78 °C → RT, 1 h, 98%; 2. I_2 (0.01 equiv.), BHT (0.1 equiv.), $CHCl_3$, Ar, RT, 2 h, 94%; (b) $KHCO_3$ (15 equiv.), BHT (0.1 equiv.), MeOH–H_2O (2 : 1), Ar, RT, 1 h, 92%; (c) $(MeO)_2CMe_2$ (2.0 equiv.), CSA (0.10 equiv.), DMF, Ar, 0 °C, 15 min, 75% yield;[7] (d) *n*-BuLi (1.00 equiv.), CO_2 (g), THF, Ar, −50 °C, 30 min, 100%; (e) Dowex 50W X8 sulfonic acid resin (2.0 mass equiv.), H_2O–THF (4 : 1), Ar, 50 °C, 3 h, 92%; (f) $MeO_2C–CH=PPh_3$ (1.1 equiv.), CH_2Cl_2, Ar, RT, 2 h, 97%, 11 : 1 (*E* : *Z*); (g) DCC (1.5 equiv.), DMAP (0.10 equiv.), CSA (0.10 equiv.), CH_2Cl_2, Ar, 0 °C, 30 min, 87%.

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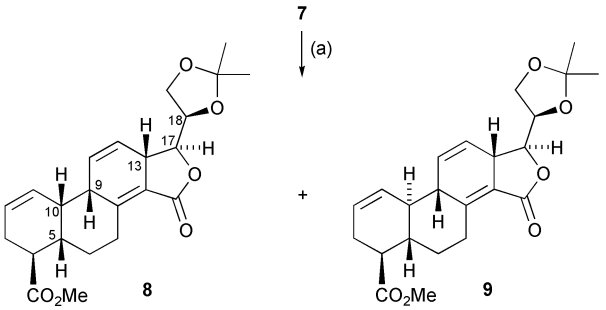


Scheme 2 The domino IMDA reaction: glucose series. *Reagents and conditions*: (a) BHT (0.1 equiv.), PhCl (5 mM in **7**), Ar, 132 °C, 45 min, 85% yield, **8** : **9** = 61 : 39.

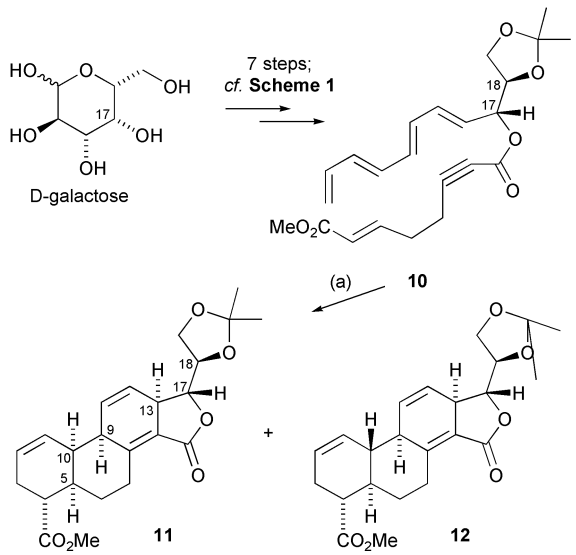
two observed products are presumably formed through *exo* and *endo* chairlike transition states of bicyclic intermediates, with the corresponding boatlike transition states not being populated to any significant extent.[4,11]

A criticism levelled against the use of sugars in the synthesis of enantiopure compounds is the inaccessibility of both enantiomeric forms.[12,13] When galactose is taken through the sequence of seven reactions described for glucose, domino IMDA precursor **10** — a diastereoisomer of **7** — is produced (Scheme 3).

This compound undergoes the domino IMDA sequence to furnish two double cycloadducts, **11** and **12**, in a ratio almost identical to that witnessed in the glucose series. The two cycloadducts from the galactose series are pseudoenantiomeric to those derived from glucose.[14] From this result it is evident that the configuration at C18 does not impact significantly upon the stereochemical outcome of the first IMDA reaction: it is the configuration at C17 that matters.

In summary, this work shows for the first time that 6/6/6/5 steroid-type tetracyclic frameworks can be prepared through a domino sequence of two IMDA reactions, that this transformation can be promoted simply by heating, and that enantiomerically pure compounds are accessible from diastereoselective IMDA processes in which a stereodirecting substituent is located in the usual position for a steroid sidechain. Application of the sequence to the synthesis of 16-oxasteroid natural products and analogues is in progress.

We thank the Australian Research Council for funding.



Scheme 3 The domino IMDA reaction: galactose series. *Reagents and conditions*: (a) BHT (0.1 equiv.), PhCl (5 mM in **10**), Ar, 132 °C, 45 min, 87% yield, **11** : **12** = 57 : 43.

Notes and references

§ *Crystal data* for **9**: Formula $C_{23}H_{28}O_6$, M = 400.45, monoclinic, space group $P2_1$(#4), a 7.8232(15), b 8.2488(16), c 15.889(3) Å, β 93.311(3), V 1023.7(3) Å^3, D_c 1.299 g cm^{-3}, Z 2, crystal size 0.398 by 0.212 by 0.050 mm, colour colourless, habit blade, temperature 150(2) Kelvin, λ(MoKα) 0.71073 Å, μ(MoKα) 0.093 mm^{-1}, T(Gaussian)$_{min,max}$ 0.966, 0.995, $2\theta_{max}$ 56.56, *hkl* range -10 10, -10 10, -20 20, N 10059, N_{ind} 2598 (R_{merge} 0.0297), N_{obs} 2070 (I > 2σ(I)), N_{var} 265, residuals* $R1(F)$ 0.0354, $wR2(F^2)$ 0.0641, GoF(all) 1.295, $\Delta\rho_{min,max}$ -0.196, 0.185 e$^-$ Å^{-3}.

*$R1$ = $\Sigma||F_O|-|F_C||/\Sigma|F_O|$ for $F_O > 2\sigma(F_O)$; $wR2$ = $(\Sigma w(F_O^2 - F_C^2)^2/\Sigma(wF_C^2)^2)^{1/2}$ all reflections

w = $1/[\sigma^2(F_O^2) + (0.02P)^2]$ where P = $(F_O^2 + 2F_C^2)/3$

For **11**: Formula $C_{23}H_{28}O_6$, M = 400.45, monoclinic, space group $P2_1$(#4), a 5.565(3), b 11.204(7), c 16.075(10) Å, β 90.682(10), V 1002.2(10) Å^3, D_C 1.327 g cm^{-3}, Z 2, crystal size 0.509 by 0.238 by 0.051 mm, colour colourless, habit plate, temperature 150(2) Kelvin, λ(MoKα) 0.71073 Å, μ(MoKα) 0.095 mm^{-1}, T(Gaussian)$_{min,max}$ 0.953, 0.995, $2\theta_{max}$ 56.56, *hkl* range -7 7, -14 14, -21 21, N 9792, N_{ind} 2503 (R_{merge} 0.0312), N_{obs} 2255 (I > 2σ(I)), N_{var} 265, residuals* $R1(F)$ 0.0349, $wR2(F^2)$ 0.0876, GoF(all) 1.190, $\Delta\rho_{min,max}$ -0.192, 0.328 e$^-$ Å^{-3}

*$R1$ = $\Sigma||F_O| - |F_C||/\Sigma|F_O|$ for $F_O > 2\sigma(F_O)$; $wR2$ = $(\Sigma w(F_O^2 - F_C^2)^2/\Sigma(wF_C^2)^2)^{1/2}$ all reflections

w = $1/[\sigma^2(F_O^2) + (0.05P)^2]$ where P = $(F_O^2 + 2F_C^2)/3$.

See http://www.rsc.org/suppdata/cc/b3/b303362g/ for crystallographic data in CIF format.

1 (*a*) P. A. Wender and B. L. Miller, *Org. Synth.: Theory Appl.*, 1993, **2**, 27–66; (*b*) T. Hudlicky, *Chem. Rev.*, 1996, **96**, 3–30; (*c*) P. A. Fuchs, *Tetrahedron*, 2001, **57**, 6855–6875.

2 (*a*) T.-L. Ho, *Tandem Organic Reactions*, Wiley, New York, 1992; (*b*) L. F. Tietze and U. Beifuss, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 131–163; (*c*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115–36; (*d*) L. F. Tietze and F. Haunert, in *Stimulating Concepts in Chemistry*, eds. M. Shibasaki, J. F. Stoddart and F. Vögtle, Wiley-VCH, Weinheim 2000, pp. 39–64.

3 Reviews of tandem cycloaddition sequences: (*a*) J. D. Winkler, *Chem. Rev.*, 1996, **96**, 167–176; (*b*) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137–165.

4 M. Norret and M. S. Sherburn, *Angew. Chem., Int. Ed.*, 2001, **40**, 4074–4076.

5 A. S. Perlin, F. Gonzalez and S. Lesage, *Carbohydr. Res.*, 1975, **42**, 267–274.

6 F. Naf, R. Decorzant, W. Thommen, B. Willhalm and G. Ohloff, *Helv. Chim. Acta*, 1975, **58**, 1016–1037.

7 A 5 : 1 mixture of monosubstituted : disubstituted dioxolanes is obtained from this reaction. The unwanted minor regioisomer was recycled through deprotection to the triol: Dowex resin (2 mass equiv.), BHT (0.10 equiv.), H_2O–THF (4 : 1), 24 h, 85%.

8 Prepared in two steps from commercially available 4-pentyn-1-ol: D. Ma and X. Lu, *Tetrahedron*, 1990, **46**, 6319–6330.

9 Reviews of IMDA reactions: (*a*) D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187–238; (*b*) W. R. Roush, in *Comprehensive Organic Synthesis*, eds. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon, Oxford, 1991, **vol. 5**, pp. 513–550; (*c*) A. G. Fallis, *Acc. Chem. Res.*, 1999, **32**, 464–474; (*d*) B. R. Bear, S. M. Sparks and K. J. Shea, *Angew. Chem., Int. Ed.*, 2001, **40**, 820–849.

10 The transition state leading to the unseen C13, C17-*syn*, isomer presumably suffers a large energetic penalty through the development of destabilizing[1,3] A strain between H12 and the dioxolane residue. For detailed discussion see C. I. Turner, R. M. Williamson, M. N. Paddon-Row and M. S. Sherburn, *J. Org. Chem.*, 2001, **66**, 3963–3969.

11 M. Ihara, A. Katsumata, M. Egashira, S. Suzuki, Y. Tokunaga and K. Fukumoto, *J. Org. Chem.*, 1995, **60**, 5560–5566.

12 For reviews on sugar-derived building blocks in synthesis, see: (*a*) S. Hanessian, *Organic Chemistry Series, Vol. 3. Total Synthesis of Natural Products: The "Chiron" Approach*, Pergamon, Oxford, 1983; (*b*) M. Bols, *Carbohydrate Building Blocks*, Wiley, New York, 1996.

13 For reviews on carbohydrate → carbocycle transformations, see: (*a*) R. J. Ferrier and S. Middleton, *Chem. Rev.*, 1993, **93**, 2779–2831; (*b*) P. I. Dalko and P. Sinay, *Angew. Chem., Int. Ed.*, 1999, **38**, 773–777.

14 The absolute configuration of each of the five newly formed stereocentres in one series is opposite to that obtained in the other.

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