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Full Paper

Efficient Synthesis of an Indinavir Precursor from Biomass-Derived (−)-Levoglucosenone

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Lignocellulosic biomass pyrolysis with acid catalysis selectively produces the useful chiral synthon 6,8-dioxabicyclo [3.2.1]oct-2-ene-4-one ((−)-levoglucosenone, LGO). In this report, LGO was used to prepare (3*R*,5*S*)-3-benzyl-5-(hydroxymethyl)-4,5-dihydrofuran-2(*3H*)-one, which is an intermediate used in the construction of antivirals including the protease inhibitor indinavir. To achieve the synthesis, the hydrogenated derivative of LGO was functionalised using aldol chemistry and various aromatic aldehydes were used to show the scope of the reaction. Choice of base affected reaction times and the best yields were obtained using 1,1,3,3-tetramethylguanidine. Hydrogenation of the α-benzylidene-substituted bicyclic system afforded a 4 : 3 equatorial/axial mixture of isomers, which was equilibrated to a 97 : 3 mixture under basic conditions. Subsequent Baeyer–Villiger reaction afforded the target lactone in 57 % overall yield for four steps, a route that avoids the protection and strong base required in the traditional approach. The aldol route is contrasted with the α-alkylation and a Baylis–Hillman approach that also both start with LGO.

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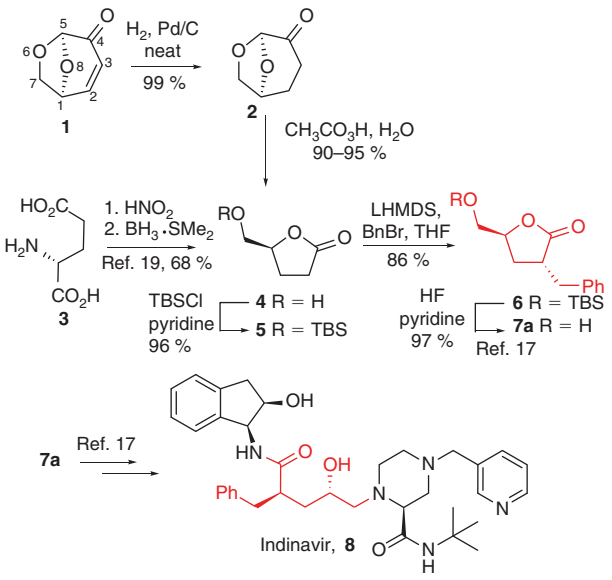
Introduction

The chiral synthon levoglucosenone[1] (**1**, 6,8-dioxabicyclo [3.2.1]oct-2-en-4-one, LGO) has recently become available in kilogram quantities owing to advances in reaction processing and separation of the product from impurities.[2] LGO can be synthesised in a single step from cellulose or lignocellulosic biomass such as bagasse or sawdust, making it attractive as a chiral pool material.[3–5] It has been used to prepare a variety of bioactive compounds,[6] carbohydrate derivatives,[7,8] and precursors for pharmaceuticals.[9] Reduction of LGO yields 6,8-bicyclo[3.2.1] octan-4-one **2** (Scheme 1), which is under development as a solvent (Cyrene™) owing to the scalability of its preparation and unique solvent properties.[10,11] The current availability of **2** and its functionality have led us to investigate the conversion of **2** into chiral γ-butyrolactones, which are important motifs in natural products and bioactive molecules.[12]

The Baeyer–Villiger reaction can be used to generate (*S*)-5-(hydroxymethyl)-4,5-dihydrofuran-2(*3H*)-one (**4**), a widely used chiral synthon, from the 6,8-dioxabicyclo[3.2.1]octan-4-one ring system.[9,13,14] The rigid bicyclic ring system in **1** and **2** can be employed for diastereoselective reactions[15] and, combined with the Baeyer–Villiger reaction, allows the synthesis of γ-lactones with a variety of substitution patterns.[16] The high migratory aptitude of the α-ketal means that excellent yields and selectivity are obtained for lactones even if α′-substitution is present.[16] The synthesis of **4** from LGO can be performed using high-yielding steps and requires no water-sensitive reagents or chromatography, which are clear advantages over the traditional route that starts with glutamic acid.[17]

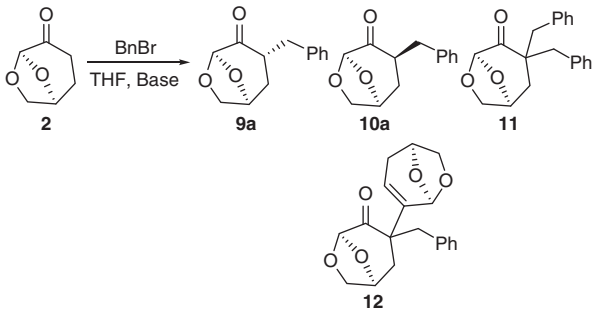
This chemistry is applicable to the synthesis of indinavir **8**, a highly active protease inhibitor developed by Merck and Co. for the treatment of human immunodeficiency virus (HIV) infection, which was until recently on the World Health Organisation (WHO) list of essential medicines.[18] The core pentanamide motif contains two chiral centres and can be constructed from (*S*)-5-(hydroxymethyl)-3-benzyldihydrofuran-2(*3H*)-one (**7a**) (Scheme 1).[17] In the original description of the synthesis



Scheme 1. Preparation of lactone **7a** from glutamic acid **3** via lactone **4** and showing its incorporation into indinavir (**8**)[17] and preparation of lactone **4** from LGO **1**.[9]

of indinavir by Dorsey et al., the pentanamide was constructed via the stereoselective benzylation of *tert*-butyldimethylsilyl (TBS)-protected γ-lactone **5**.[17] This procedure required a five-step synthesis starting with glutamic acid, a borane reduction to obtain the alcohol **4**,[19] and anhydrous conditions with strong base for the benzylation reaction. The commercial route to indinavir now avoids the use of **7a**, and instead constructs the pentanamide using the allylation of a 3-phenylpropanamide derivative.[20,21] Recent patents describing bioactives synthesised incorporating **7a** have used the strategy of Dorsey et al. to construct **7a**, which indicates that this is still the best-known route to this lactone.[22] Lactone **7a** has also been used for the synthesis of protease inhibitors active against indinavir-resistant virus,[23] vasoactive intestinal peptide receptor inhibitors,[22] and allylamides useful for the treatment of Alzheimer's disease.[24] The importance of lactone **7a** in the medicinal chemistry literature led us to investigate methods to synthesise it from LGO, but our previous attempts to insert benzyl groups on the 3-iodide derivative of LGO using Suzuki–Miyaura chemistry were not successful.[16] We now report on the efficiency of three different approaches for the synthesis of lactone **7a** using LGO, and the development of a general strategy for the preparation of 3-(arylmethyl)-6,8-dioxabicyclo[3.2.1]octanones.

Table 1. Alkylation reactions of 2 with benzylbromide



BnBr equiv.	Base	Temp. [°C]	Time [h]	Yield[A] (**9a** : **10a** : **11**)
1.1	LDA[C]	−78 to 25	48	7 (1 : 3 : 26)[B]
1.0	^{t}BuOK	25	24	31 (3 : 2 : 95)
2.4	^{t}BuOK	25	1.5	88 (0 : 0 : 100)

[A]Isolated yield with ratio determined by gas chromatography–mass spectrometry (GC-MS).
[B]16 % of adduct **12** was also isolated.
[C]LDA = lithium diisopropylamide.

Results and Discussion

We envisaged that the synthesis of lactone **7a** could be approached using direct alkylation of an enolate, aldol chemistry to introduce a benzylidene at the α-position of **2**, or Baylis–Hillman chemistry starting with LGO, the key step being the C–C bond forming reaction at the α-centre. Watson et al. recently reported that **2** undergoes aldol reactions to form a dimer in the presence of base, providing support for an aldol approach to generate **7a**.[11] Furthermore, LGO is known to undergo a stereoselective domino oxa-Michael–aldol reaction with water and aromatic aldehydes, which would involve similar reactivity.[25,26]

The conceptually simplest approach to the α-benzylated derivatives via α-alkylation of ketone **2** consistently failed to give appreciable amounts of monoalkylated products **9a** or **10a** and reactions were dominated by the dibenzylated product **11** (Table 1). Lowering the temperature and using a strong base afforded mainly dibenzylated adduct **11** as well as compound **12**, which presumably resulted from a dimerisation of **2**, subsequent γ-deprotonation, and alkylation. The propensity for dialkylation led us to increase the number of equivalents of halide; a very good yield of the dialkylated adduct **11** was obtained. Thus, the α-alkylation reaction was an excellent way to dibenzylate the carbon adjacent to the carbonyl in **2**, but efficient mono-α-benzylation of the ketone using benzyl bromide and base was not possible.

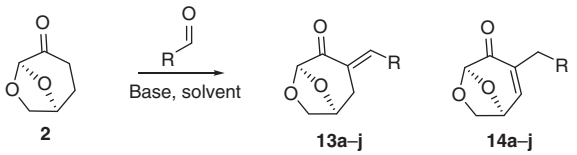
Turning our attention to the aldol reaction, an optimisation study for the reaction of **2** with benzaldehyde was performed and representative reactions are shown in Table 2. Initial attempts using K_2CO_3 and NEt_3 as base gave either none or very little aldol adduct (Table 2, entries 1–3). Switching the base to 1,1,3,3-tetramethylguanidine (TMG), an excellent yield of benzylidene was obtained; however, reactions took 24–48 h to reach completion. Eliminating the solvent and running the reactions neat gave a better yield of **13a** and reduced the reaction time to just 1 h. The geometry of the alkene in **13a** was assigned as *E* on the basis of a cross-peak in the 2D NOESY spectrum between the aromatic ring protons and the methylene at C2. It should also be noted that photochemical isomerisation of the *E*-enone to the *Z*-enone was observed over time, requiring the products to be kept in the dark.

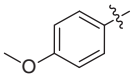
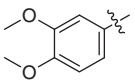
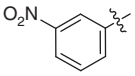
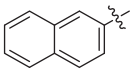
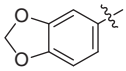
With the success of the aldol reaction of **2** with benzaldehyde, we attempted to extend the derivatisation to other types of aldehydes. Not only could these materials be used to construct analogues of indinavir or the other bioactives prepared from lactone **7a**, the preparation of new chiral materials from such an abundant precursor could lead to new chiral ligands or catalysts. Thus, ketone **2** was reacted with a series of aromatic aldehydes as shown in Table 2 to give the enones **13b**–**13i** in moderate to excellent yield. Although successful for the parent aldol reaction, the neat reaction conditions were found to be unsatisfactory for other aldehydes examined both in yield and product distribution.

In addition to the aldol adducts, some double-bond migration was observed, giving endocyclic enones **14b**, **d**, **f**–**h**, which were evident in the ^{1}H NMR spectra of crude reaction mixtures. These products lacked the H2α and H2β signals normally seen between δ 2.5 and 3.5 ppm in the ^{1}H NMR spectrum, which were replaced with a benzylic AB quartet at δ 3.60–3.70 ppm. The migration was more pronounced in reactions with aromatic aldehydes substituted with electron-withdrawing groups (Table 2, entries 10 and 19). We found that the isomerisation was virtually eliminated when the reaction was performed in acetonitrile at 50°C and the amount of base was also limited. The installation of an alkyl group using butyraldehyde was also attempted; however, the yield of alkylidene **13j** was poor, indicating that an aldol approach was not feasible for alkyl substituents.

To access these allylic rearrangement products, the isomerisation of **13b** to *endo*-alkene **14b** was attempted. No isomerisation was observed when **13b** was heated in neat Hünig's base at 80°C; however, isomerisation was observed by heating in TMG at 100°C, although the reaction was slow and significant decomposition occurred, making isolation difficult. Thus, heating **13b** at 100°C for 48 h with TMG gave **13b**/**14b** with a ratio of

Table 2. Aldol condensations with 2 with aldehydes

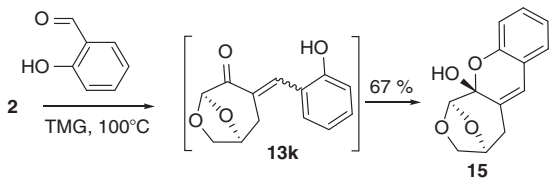


Entry	R	Equiv. RCHO	Solvent	Temp. [°C]	Base (equiv.)	Time [h]	Product	Yield (**13** : **14**)[A]
1	Ph	1.5	Dioxane	25	K_2CO_3 (1.0)	72	**13a/14a**	Trace (ND[E])
2		1.5	Dioxane	70	K_2CO_3 (1.0)	24	**13a/14a**	Trace (ND)
3		1.5	MeCN	70	NEt_3 (1.0)	72	**13a/14a**	11 (ND)
4		1.5	THF	70	TMG (2.0)	24	**13a/14a**	75 (ND)
5		1.5	Dioxane	70	TMG (1.0)	45	**13a/14a**	78 (ND)
6		1.5	MeCN	70	TMG (1.0)	45	**13a/14a**	74 (ND)
7		1.5	DMSO	70	TMG (1.0)	18	**13a/14a**	84 (99 : 1)
8		2.0	–	100	TMG (2.0)	1	**13a/14a**	82 (99 : 1)
9		1.3	–	100	TMG (0.2)	9	**13a/14a**	84 (99 : 1)
10		1.2	–	100	TMG (1.0)	2.5	**13b/14b**	32 (8 : 25)
11		1.1	MeCN	50	TMG (0.1)	17.5	**13b/14b**	82 (>99 : 1)
12		1.2	–	100	TMG (1.0)	1.5	**13c/14c**	58 (>99 : 1)
13		1.1	MeCN	50	TMG (1.0)[B]	96	**13c/14c**	57 (93 : 7)
14		1.2	–	100	TMG (1.0)	20	**13d/14d**	60 (10 : 1)
15		1.1	MeCN	50	TMG (1.0)[B]	140	**13d/14d**	58 (>99 : 1)
16		1.2	MeCN	50	TMG (0.1)	24	**13e/14e**	90 (>99 : 1)
17		1.2	–	100	TMG (1.0)	43	**13f/14f**	30 (25 : 6)
18		1.1	MeCN	50	TMG (1.0)[B]	100	**13f/14f**	53 (>99 : 1)
19		1.2	–	100	TMG (1.0)	3.5	**13g/14g**	11 (20 : 11)
20		1.1	MeCN	50	TMG (0.1)	16.5	**13g/14g**	87 (>99 : 1)
21		1.2	–	100	TMG (1.0)	1.5	**13h/14h**	61 (>99 : 1)
22		1.1	MeCN	50	TMG (0.1)	110	**13h/14h**	15 (50 : 3)
23		1.1	–	100	TMG (1.0)	6.5	**13i/14i**	48[C] (>99 : 1)
24	^{n}Bu	1.0	MeCN	50	TMG (0.1)	16	**13j**	22[D]

[A]Isolated yields with ratios determined using GC-MS.
[B]Additional TMG was added during the course of the reaction to bring the number of equiv. from 0.1 to 1.0.
[C](*E*)-**13i** : (*Z*)-**13i** = 50 : 11 by GC-MS.
[D]**13j** was not separable from unidentified impurities.
[E]ND = not determined.

1 : 4, which was comparable with that obtained using the neat reaction conditions for 2.5 h (Table 2, entry 10). Transition metal-catalysed processes are known for isomerisation of an exocyclic double bond into a ring giving cyclic α,β-unsaturated ketones;[27] however, further examination of this isomerisation was beyond the scope of the present work.

The reaction of **2** with salicylaldehyde afforded hemiketal **15** containing a *Z*-double bond in excellent yield (Scheme 2). Under the reaction conditions, some *E* to *Z* isomerisation of the alkene in **13k** presumably occurred and subsequent cyclisation by addition of the phenol to the ketone resulted in a stable hemiketal. The stereochemistry of the alcohol is suggested owing to the preferred α-facial addition of nucleophiles to the ketone in **2**.[28] Furthermore, the alcohol formed by the addition to the α-face can hydrogen bond with the neighbouring axial O-6, which would further stabilise hemiketal **15**.

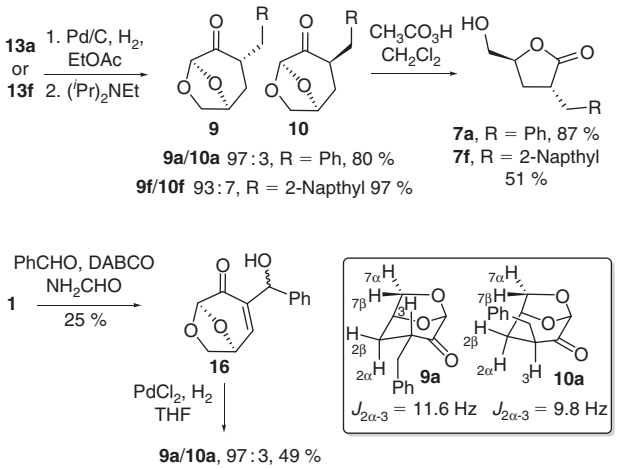


Scheme 2. Aldol reaction of **2** with salicylaldehyde.

The conversion of **13a** through to the lactone **7a** was investigated using hydrogenation conditions and is contrasted with a Baylis–Hillman strategy starting with LGO in Scheme 3. The Pd/C-mediated hydrogenation of benzylidene **13a** afforded a mixture with significant amounts of **10a** consistent with the hindrance encountered on the β-face of the bicyclic ring system. The isomerisation of **10a** to the more stable equatorially oriented **9a** was achieved by stirring the mixture in Hunig's base and gave a 97 : 3 ratio of isomers at equilibrium. This two-step approach gave consistently higher yields than the hydrogenation of **13a** using $PdCl_2/H_2$, which afforded 45 % of **9a** with the isomerisation of **10a** to **9a** promoted by the HCl liberated on catalyst activation. Conversion through to lactone **7a** was achieved using peracetic acid in 87 % yield and traces of the diastereomer were removed by crystallisation. Matching the spectroscopic data obtained for **7a** with the literature[17] confirmed that the assigned stereochemistry for the intermediate **9a** was correct. Similarly, the synthesis of 2-napthyl-substituted lactone **7f** proceeded through the mixture of **9f** and **10f**, although the isolated yield of **7f** was low following Baeyer–Villiger reaction owing to difficulties removing the minor isomer.

The NMR spectra, and in particular the coupling constants for the ring protons of the reduction products **9a** and **10a**, warrant discussion. Cross-peaks between H3 (2.85 ppm) and H7β (3.90 ppm) in the 2D NOESY NMR were consistent with the assigned stereochemistry of **9a**. The C2 methylene in **9a** appeared as a non-first-order multiplet; however, NOESY interactions of H2β with H7β allowed the differentiation of H2α (downfield) and H2β (upfield) in the multiplet. As expected for a chair-like conformation, a large $J_{H3–H2\alpha}$ coupling (11.4 Hz) was observed indicating a *trans*-diaxial relationship for these protons. In the isomer **10a**, a W-path ^4J coupling between H7α (3.73 ppm) and H2α (2.27 ppm) was used to assign H2α. Surprisingly, **10a** also exhibited large coupling constants between H3 and H2α ($J_{H3–H2\alpha}$ 9.8 Hz). A chair-like conformation for **10a** should have given a small coupling constant (4–7 Hz) between H3 (2.75 ppm) and H2α and the observed coupling of 9.8 Hz indicates a distorted ring for **10a**. Steric interactions of the benzyl substituent at C3 and the bridging methylene ether may cause the six-membered ring to flatten, which closes the H2α–C2–C3–H3 dihedral angle, explaining the observed coupling constants.

It was envisaged that the sequence from LGO to **7a** could be shortened if a Baylis–Hillman reaction was used to construct the α-C–C bond. LGO has been employed in Baylis–Hillman reactions crossed with aliphatic aldehydes promoted by diethylaluminium iodide;[29,30] however, there are no examples in the literature of successful reactions of LGO with aromatic aldehydes. A survey of Baylis–Hillman conditions for the reaction of **1** with benzaldehyde resulted in either no reaction or low yields of product, with the best yield of 25 % obtained when the reaction was promoted by formamide/1,4-diazabicyclo[2.2.2]octane (DABCO).[31] A proof-of-principle conversion of LGO



Scheme 3. Preparation of **7a** and **7f** from **9a**.

into **7a** via the mixture of diastereomers **16** was thus achieved in three steps when **16** was hydrogenated using $PdCl_2/H_2$ (Scheme 3). The yields obtained for the Baylis–Hillman reaction were low, and the hydrogenation gave a mixture requiring chromatography; however, a variety of catalysts are available for this reaction and if optimised, it could be the preferred route.

Conclusions

This report described the α-functionalisation of the 6,8-dioxabicyclo[3.2.1]octan-3-one ring system using aldol reactions. Subsequent reduction of the products and then Baeyer–Villiger reaction afforded the valuable lactone **7a** in an overall 57 % yield from LGO. The preparation of **7a** could also be achieved in only three steps from LGO, albeit in low yield, using a Baylis–Hillman approach. These compounds have previously been used to synthesise the antiviral compound indinavir and a range of other protease inhibitors, which demonstrates the utility of this chemistry.

Supplementary Material

All experimental procedures, spectral data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds are available on the Journal's website.

Conflicts of Interest

The authors declare no conflicts of interest.

Acknowledgements

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