Tetrahedron xxx (2013) 1–9

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

$Bi(OTf)_3$—a mild catalyst for the synthesis of difficult to obtain C-alkyl substituted glycolurils

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ARTICLE INFO

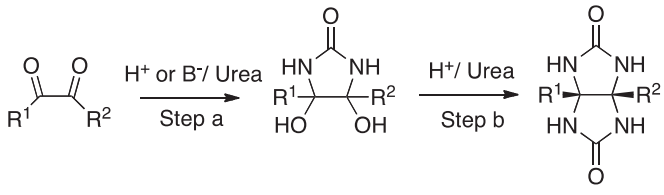
Article history:
Received 15 July 2013
Received in revised form 5 September 2013
Accepted 24 September 2013
Available online xxx

ABSTRACT

We have employed $Bi(OTf)_3$ (5 mol %) a catalyst not previously used in the synthesis of urea condensation products from α-dicarbonyl compounds, as a mild method for the synthesis of difficult to obtain glycolurils. There are limited synthetic examples of *C*-alkylated substituted glycolurils and even fewer carrying functionality on the alkyl substituent. We have successfully synthesised some challenging examples of glycolurils with functionality, which include norbornyl-based structures. The milder reaction conditions enables the isolation of defined intermediate diols and ureas in good yields, and glycolurils are possible, where they would not normally be available under conventional acid catalyzed conditions.

1. Introduction

Since the beginning of the 20th century researchers have found stimulation in the chemistry of the family of bicyclic ureides known as glycolurils **3** (Scheme 1).[1–14] These compounds and their derivatives have been used as building blocks in the synthesis of pharmaceuticals,[15] biomimetic templates,[16] the synthesis of cucurbit[*n*]uril[3,10,11,13,14,17] and various supramolecular self-assembled structures, such as molecular clips, clefs and cavities.[4–9,12] The particular chemical and structural features of glycolurils that make them interesting are their mildly nucleophilic ureide N, their concave faces that are inherent in the *cis*-fused structure of two imidazolidin-2-one rings, and in combination with their concave faces H-bond donor NH and acceptor C=O functional groups (Fig. 1). It is these latter features that have captured the imagination of supramolecular chemists in the quest to understand the behaviour of spaces created within glycoluril derived supramolecular structures.[4–9,12,18] More recently glycolurils have become particularly important to the synthesis of the family of molecular hosts, the cucurbit[*n*]uril and their analogues.[8,10,11,13,14,17] Of special interest is the introduction of substitution into cucurbit[*n*]uril through the use of substituted glycolurils as synthetic building blocks. Specifically, substitution at the *cis*-fused junction (C3a and C6a see Fig. 1) of the glycolurils provides a building block that translates into equatorial substitution of cucurbit[*n*]uril.[10,11,13,17,19,20]



1a $R^1 = R^2 = (CH_2)_3$
1b $R^1 = R^2 = 3\text{-}CH_3(CH_2)_3$
1c $R^1 = R^2 = (CH_2)_4$

Scheme 1. General reaction to glycolurils from α-dicarbonyl compounds.

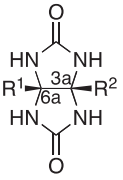


Fig. 1. Glycoluril.

The basic approach to the synthesis of glycolurils is through the acid catalysed condensation of a urea and a α-dicarbonyl compound (Scheme 1). It is the choice of α-dicarbonyl compound that can potentially provide a desired substitution on the glycoluril but in practise many C-alkyl and functionalised substituents are currently unavailable or limited by poor yields. Some substituted glycolurils have proved useful for the synthesis of new substituted cucurbit[*n*]uril and their analogues but very few carry functionality.[8,10,11,13,20]

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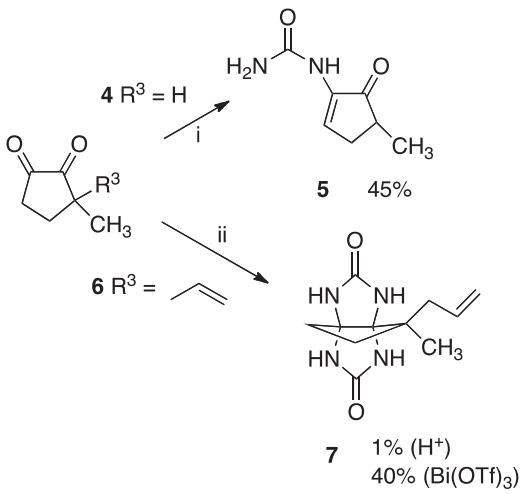
0040-4020/$ – see front matter © 2013 Published by Elsevier Ltd.
http://dx.doi.org/10.1016/j.tet.2013.09.071

In this study we examine the synthesis of a group of five-membered carbocycles as potential substituents at the C3a and C6a fused junction of the glycoluril framework with a view to also introducing a functional group. To this objective we report the first examples of glycolurils synthesised using $Bi(OTf)_3$ as a catalyst and highlight substantial synthetic improvements over traditional acid catalysts normally used for the synthesis of glycolurils. Recently heteropolyoxometalates have been reported as potential catalysts for the synthesis of glycolurils but the demonstrated examples were relatively trivial and carried no functional groups.[28]

2. Results and discussion

The generally accepted reaction process in the synthesis of a glycoluril **3**, involves the reaction intermediate diol **2** as the first condensation product in a two-step reaction (Steps **a** and **b**) starting from an α-dicarbonyl compound (ketone or aldehyde) (Scheme 1).[1,21,22] In the presence of 2 equiv of urea and an acid catalyst, steps **a** and **b** proceed without interruption via dehydration and condensation of a second molecule of urea to give the glycoluril **3**. However, we have found that alternative products can result at either step ***a*** or ***b*** that prevents the formation of **3**. We were motivated to understand the types of side-reactions that can occur in order to develop conditions to avoid them. Our exploration focused on synthesising **3** where R^1 and R^2 are C-alkyl substituents that can carry functionality. Initially we investigated the glycoluril condensation reaction under conventional acid catalysed conditions (aqueous acid HCl, anhydrous HBF_4 etherate and TFA) and then selected examples were evaluated where, $Bi(OTf)_3$ was used as the catalyst. In recent years $Bi(OTf)_3$ has attracted considerable interest as an effective Lewis acid for a variety of reactions and has the added advantages of low cost, low toxicity and reasonable stability.[29–31] We have found that this catalyst is very effective for the synthesis of glycolurils giving cleaner results, higher yields and at lower temperatures.

1,2-Cyclopentadione (**1a** $R^1{=}R^2{=}(CH_2)_3$), which carries no substituents or functionality has been reported to give the glycoluril **3a** under traditional conditions but the yields were poor.[23,24] The commercially available 3-methyl-1,2-cyclopentadione (**1b** $R^1{=}R^2{=}$3-Me$(CH_2)_3$) under similar acid catalysed conditions (Scheme 1) gave a complex mixture from which, neither **2b** nor **3b** ($R^1{=}R^2{=}$3-Me$(CH_2)_3$) could be detected. However, the urea condensation product **5** was isolated, which demonstrates a divergent reaction path involving the formation of an endocyclic double bond in the substituent ring (Scheme 2). This alternate reaction path cannot easily lead back to glycoluril **3b**.[25] A divergent path of this type has been previously reported as a deliberate reaction process for the six-membered carbocyclic ring substituent derived from the imidazolidinone **2c** (**1c** to **2c** $R^1{=}R^2{=}(CH_2)_4$).[25]



Scheme 2. (i) Urea, TFA and benzene reflux 4 h. (ii) Urea, HBF_4 etherate and benzene reflux 4 h; or $Bi(OTf)_3$ as catalyst.

It was speculated that the enol tautomer, thermodynamically favoured to occur at the methyl substituted position, was in some way responsible for the product outcome of **5**. Blocking this possibility as in diketone **6** gave the glycoluril **7**, albeit with a very low yield (Scheme 2). The remaining reaction product material was a complex mixture indicating that perhaps a number of divergent paths were operating. Repeating the same condensation reaction with $Bi(OTf)_3$ (5 mol %) as the catalyst gave a 40% yield, a large improvement.

Applying the $Bi(OTf)_3$ catalysed conditions to an acyclic example where the divergent path to a double bond is prevented as in the case of the keto-aldehyde **8** the yield was again almost doubled compared to the traditional acid catalysis (Scheme 3, Table 1). However, an alternative divergent path occurs where a portion of the intermediate diol **9a** most likely hydrolyses and cyclises to form product **9** (36%). This perhaps indicates a difficulty in the ring closure of **10a** at the neopentyl C-centre.

The blocking of double bond formation to prevent a divergent pathway carries with it steric penalties, impeding the reaction beyond **9a** leading to the formation of **9** (the furan ring formation was confirmed by a ^1H NOESY spectrum S19).

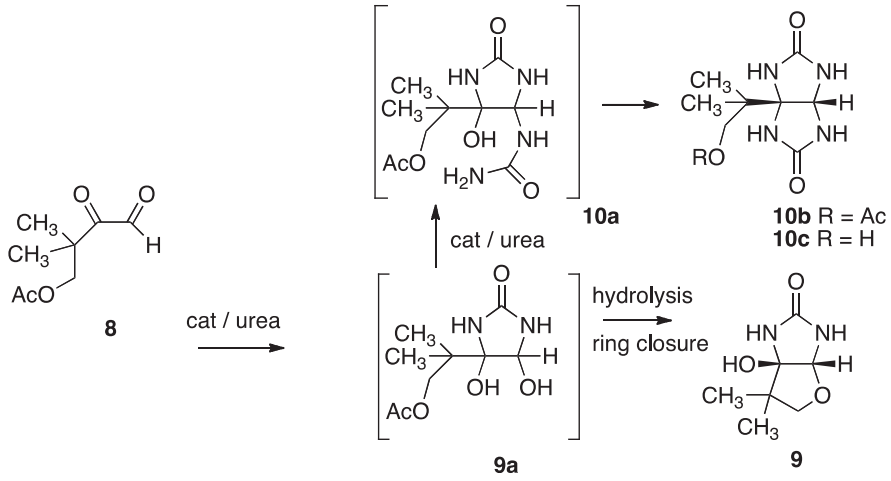
This steric penalty was also found in the urea condensation reaction of camphorquinone (**11**). This reaction has been reported to condense with urea under acid catalysed conditions similar to those outlined in Scheme 1 using a protic acid catalyst, to give a glycoluril but there is limited experimental detail and no reported spectroscopic data.[24] In our hands the reaction proceeds in the presences of TFA as the acid catalyst to give the glycoluril **12** (Scheme 4) but only if the reaction temperature is at least 140 °C. At a lower temperature of 80 °C (refluxing benzene) the imidazolidinone urea product **13**, was formed. This intermediate is indicative of the primary condensation of the second molecule of urea of step **b** of the general reaction process previously discussed but incomplete (Scheme 1). The lower temperature appeared to be insufficient to overcome the steric constraint imposed by the 1-methyl group of the camphor structure. However, returning the imidazolidinone urea **13** to acidic (TFA) xylene or formamide at temperatures of >110–140 °C, the ring closure is completed and the glycoluril **12** was produced. It should be noted that the intermediate **13** is similar in structure to the proposed intermediate **10a** of Scheme 3.

As with the previous examples discussed, $Bi(OTf)_3$ as the catalyst resulted in a doubling of the yield and at a temperature 60 °C lower (Table 1).

Given that camphorquinone (**11**) condenses with urea to produce the glycoluril **12**; we therefore expected that norbornane derivatives would react in a similar way. A series of O functionalised norbornane diones **14**, **17a**–**d** were compared under traditional acid catalysis and $Bi(OTf)_3$ conditions (Schemes 5 and 6). There were three striking product differences—TFA catalysis gave predominantly the diol intermediates as indicated at step ***a*** of the general Scheme 1 for diones (Schemes 5 and 6)—the yields of the diols were dramatically increased with $Bi(OTf)_3$ as catalyst (>three times)—no glycolurils could be synthesized from any of the diones **14**, **17a**–**d** unless the catalyst was $Bi(OTf)_3$ and even then only the glycolurils **20c** and **20d** were obtained (Table 2 and Scheme 7).

Given that our objective was the preparation of *O* substituted norbornyl glycolurils we prepared the *exo*,*exo* 5,6-dibenzoatedione **17a**[27] in order to derive a symmetrically substituted glycoluril. However, all attempts to synthesise a glycoluril from **17a** using acid catalysis gave only the imidazolidinonediol **18a** or decomposition (Scheme 6). No steric constraint was expected from the two C5 and

Please cite this article in press as: Wu, F.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.09.071

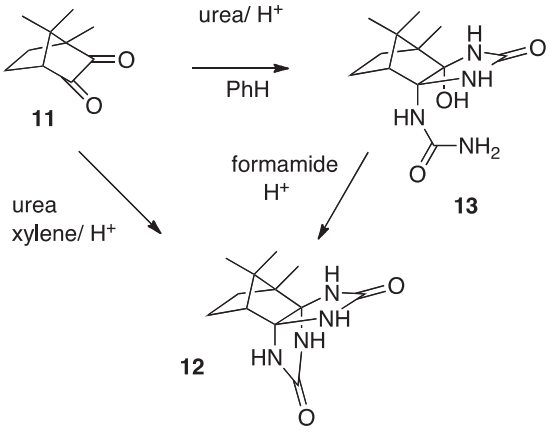


Scheme 3. Water (pH 1)/THF several days rt or $Bi(OTf)_3$ in benzene at rt.

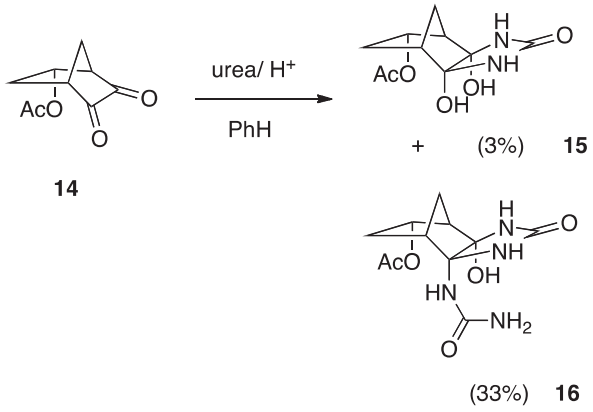
Table 1
Comparison of the differences between catalysts types (H^+/$Bi(OTf)_3$) and temperature in the condensation reaction to glycoluril

α-dicarbonyl	Glycoluril	Yield %[a] H^+/$Bi(OTf)_3$	Temp °C
6	**7**	1[b]/40	110 (2 h)
8	**10b**	23[c]/39[d]	rt (5 d)
11	**12**	15[e]/30[f]	140/80

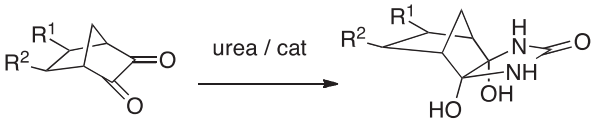
[a] Isolated yields.
[b] Refluxing toluene for both cat, H^+=HBF_4Et_2O. TFA gave no product.
[c] H^+=dilute HCl 0.1 M/THF (2.5:1); no product with TFA in toluene.
[d] Benzene or toluene.
[e] Refluxing xylene 4 h, extended times gave decomposition.
[f] Refluxing benzene 20 h.



Scheme 4. The catalysed condensation of camphorquinone (**11**) with urea, under different solvent and temperature conditions (H^+=TFA). The same products were obtained with $Bi(OTf)_3$ as the catalyst (see text for details).



Scheme 5. The acid catalysed condensation of dione **14** with urea, H^+=TFA.



	A	B
17a R^1 = R^2 = OBz	**18a** (24%)	
17b R^1 = OBz, R^2 = H	**18b** (28%)	(82%)
17c R^1 = R^2 = H	**18c** (17%)	(85%)
17d R^1 = R^2 = CH_2OAc	**18d** (20%)	

Scheme 6. **A** TFA catalyzed urea condensation reactions of norbornane-2,3-dione and some *exo O* substituted derivatives and **B** $Bi(OTf)_3$ catalyzed.

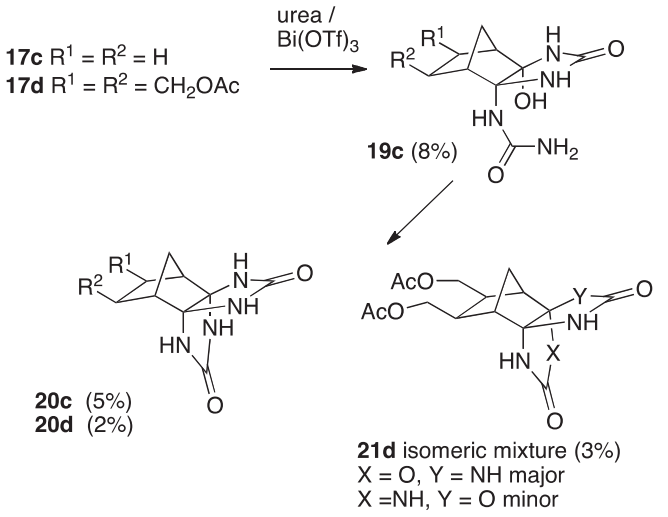
C6, *exo* benzoate groups but in order to test this, we prepared the mono C5 *exo* benzoate **17b**. Under identical reaction conditions the result was the same where imidazolidinonediol **18b** was the only product. Two more examples were compared, the norbornadione **17c** with no substituent groups and the *endo* 5-acetate **14**.[26] Curiously **17c** with no substituent groups, again gave the imidazolidinonediol **18c**, while **14** afforded the imidazolidinonediol **16** but only under shorter reaction times and only as a minor component. The major product from the condensation reaction of **14** was the imidazolidinone urea **16** (33%, Scheme 5). NOESY spectra of **16** revealed unequivocally that the imidazolidinone ring was *exo*. None of the desired glycoluril product was found. Clearly it is the second step to the condensation reaction (Step **b**) that is more difficult, requiring replacement of the OH and the introduction of the *endo* urea group prior to cyclisation to complete step **b**. It is however, perplexing that the *endo* 5-acetate **14** should condense with the second molecule of urea while diones **17a**–**b** did not. Cyclisation of **16** to give a glycoluril was not observed.

The urea condensation reaction of diones **17b**–**d** were subjected to the $Bi(OTf)_3$ catalysed conditions and it was found that under mild conditions **17b** (2.5 h refluxing toluene) and **17c** at rt (2 h in

Table 2
Comparison of the catalysts TFA and $Bi(OTf)_3$ in the urea condensation reaction with several norbornyl-1,2-diones

Norbornyl-1,2-dione	Diol (%)[a]	Glycoluril[f] (%)
14	**15** (3[b]/—[c])	—[c]
17a	**18a** (24/—[c])	—
17b	**18b** (28/82[d])	—
17c	**18c** (17/85[e])	**20c** (**5%**)[b]
17d	**18d** (20/—)	**20d** (**2%**)

[a] Different catalyst condition TFA versus $Bi(OTf)_3$, respectively (isolated yields %).
[b] Major product **16** from **14** (33%), **19c** from **17c** (8%).
[c] Reaction not performed with $Bi(OTf)_3$.
[d] 2.5 h toluene reflux.
[e] 2 h in toluene at rt.
[f] Refluxing toluene 24–40 h.

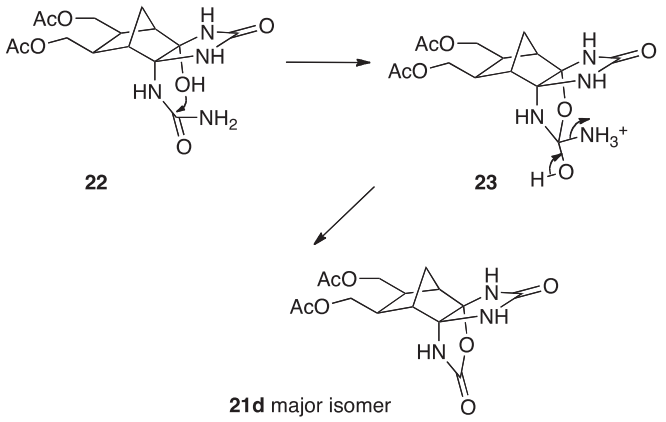


Scheme 7. $Bi(OTf)_3$ catalysed urea condensation reactions of diones **17c** and **17d** in refluxing toluene 24–40 h.

toluene) gave the corresponding diols **18b** and **18c** in isolated yields >three times that of acid catalysis (82 and 85%, respectively) (Scheme 6, Table 2). At higher temperatures and extended reaction times (refluxing toluene, 24–40 h) the two glycolurils **20c** and **20d** were obtained from diones **17c** and **17d**, respectively (Scheme 7, Table 2). While the isolated yields were low (5 and 2%, respectively) the reaction conditions have not been optimised. The limited amount of isolated product is mostly a reflection of the difficulty of the reaction, as well as a reflection of the difficulty of purification. Both glycolurils **20c** and **20d** could not be crystallised until highly pure, and both had similar polarities on silica to the polarities of their urea side-products and unreacted urea.

In addition to these technical limitations, a new side-product, the oxazolidinone **21d** as a mixture of isomers was also isolated from the $Bi(OTf)_3$ catalysed urea condensation reaction of dione **17d** (3% isolated yield) (Scheme 7). The ^1H NMR spectrum of the crude reaction mixture showed that the oxazolidinones **21d** were predominant (ratio 8:2, of **21d** relative to **20d**). The glycoluril **20d** and the oxazolidinones **21d** differ empirically ($C_{15}H_{20}N_4O_6$ and $C_{15}H_{19}N_3O_7$, respectively) by only one mass unit, however, these two compounds were readily identified by ESMS. Characteristically ESMS gives ions of H^+ or Na^+ adducts of **20d** and **21d**, where the parent compound also occurs as a dimer, which provided support with a greater mass discrimination (glycoluril **20d**: 353 [M+H^+], 375 [M+Na^+], 705 [2M+H^+], 727 [2M+Na^+]; oxazolidinones **21d**: 354 [M+H^+], 376 [M+Na^+], 707 [2M+H^+], 729 [2M+Na^+]). The distinguishing feature in the ^1H NMR spectrum arose through the lack of symmetry in the oxazolidinones **21d** with three different NH proton resonances for the major isomer, δ 8.80, 7.86 and 7.63 (the minor oxazolidinone ring isomer showed three similar but minor NH resonances, see experimental). In addition, **21d** had a significant downfield shift for the NH consistent with an oxazolidinone. The glycoluril **20d** only showed two NH resonances δ 7.11 and 7.30, comparable to the chemical shifts of the resonances of glycoluril **20c**. Further support was found in the ^{13}C NMR spectrum, which showed a resonance for 3a-C at δ 100.0 (minor isomer 101.3) consistent with the quaternary carbon substituted by N and O, and not 2× N.

It seems reasonable to conclude that the oxazolidinones **21d** are formed from an intermediate urea, such as **22** and this undergoes ring closure via an alternative route to glycoluril formation. A likely explanation is that, in competition with dehydration and urea N addition (Scheme 7), the catalytic process favours hydroxyl O addition to the urea carbonyl instead, followed by deamination as depicted in Scheme 8. Curiously the *exo* isomer of **21d** (Scheme 7) is form as a minor product suggesting an inversion of the hydroxyl group in **22** and then a similar condensation. We were unable to separate the isomers.



Scheme 8. A possible explanation for the formation of the oxazolidinone **21d**.

The determination of the precise mechanism to the oxazolidinone **21d** was beyond the scope of this study and was not pursued further.

3. Conclusion

We have successfully demonstrated the effectiveness of the catalyst $Bi(OTf)_3$ for the preparation of glycolurils normally unobtainable using convention acid catalysed conditions. It has also been demonstrated that some glycolurils that could previously only be obtained in low yields can now be produced in moderate yields. In addition to improved yields via the $Bi(OTf)_3$ catalysed process, the reaction conditions are milder and effective for the synthesis of imidazolidinonediols and imidazolidinone ureas as intermediates en route to gylcolurils. These diols and ureas can be obtained in good to high yields and may also provide opportunities to useful imidazolidinone derivatives in the future.

The results of this study suggest a potential to achieving many other C-alkyl substituted glycolurils previously unobtainable.

4. Experimental section

4.1. General

The starting materials, such as camphorquinone, the epimeric mixture of *endo* (~90%) 5-norbornen-2-yl acetate, 2,3-norbornene,

3-methyl-1,2-cyclopentadione and 3-methyl-2-butanone were purchased from commercial sources and were used without purification. DMSO, CH_2Cl_2, Et_3N, THF and pyridine were dried and freshly distilled before their use. NMR spectra were recorded at 400 MHz for the ^1H nuclei and 100 MHz for the ^{13}C nuclei. Chemical shifts are reported with the solvent as the internal standard ($CDCl_3$ δ 7.26 and 77.2 ppm, DMSO δ 2.50 and 39.5 ppm ^1H and ^{13}C, respectively).

Phase-sensitive NOESY spectra were acquired using 2048 data points in t2 for 256 t1 values with a pulse repetition delay of 1.7 s for mixing times of 350 ms. COSY experiments were acquired using 2048 data points in t_2 (with a spectral width of 4200 Hz) for 256 t_1 values with pulse repetition delay of 1.7 s with 16–128 scans per FID. All NMR experiments were conducted at 25 °C unless otherwise stated.

4.2. Preparation of starting materials

*4.2.1. 1-Butyl-2,2-dimethyl-3,4-dioxo acetate (**8**).* Starting material **8** was prepared by a modifying the procedure of Boeykens.[32] 3-Methyl-2-butanone (10 mL, 93.6 mmol) and paraformaldehyde (3.10 g, 103 mmol) were combined in glacial acetic acid (30 mL) and *p*-toluenesulfonic acid (2 crystals) was added. The mixture was then heated to reflux. After 7 h an additional portion of paraformaldehyde (330 mg) was added and the heating continued for an addition 4 h. The mixture was poured into water (100 mL) extracted with ether (3×30 mL), the combined ethereal extracts were washed with satd aqueous $NaHCO_3$ solution 3× until effervescence ceased. The ethereal extract was dried over $MgSO_4$, and the solvent evaporated in vacuo to afford an oil (9.65 g) as mixture of *1-butyl-2,2-dimethyl-3-oxo acetate* (90%) and the starting ketone (10%). The starting material was removed by bulb-to-bulb distillation. Selenium dioxide (1.40 g) was added to a solution of *1-butyl-2,2-dimethyl-3-oxo acetate* (2.00 g, 12.7 mmol) in glacial acetic acid (10 mL) and the mixture heated under reflux for 16 h. After cooling to room temperature the selenium metal was removed by filtration and washed with acetic acid. The acetic acid was removed in vacuo from the filtrate to give **8** as a yellow oil (1.75 g, 80%). This material was used in the next procedure without further purification. ^1H NMR ($CDCl_3$) δ: 9.25 (1H, s, C*H*O), 4.30 (2H, s, *CH*$_2$), 2.00 (3H, s, O*Ac*), 1.26 (6H, s, *CH*$_3$).

endo/*exo* (~8:1) bicyclo[2.2.1]heptan-5-yl-2,3-dioxo acetate (**14**) was prepared from the commercially available epimeric mixture of *endo* (~90%) *exo* 5-norbornen-2-yl acetate by the procedure of Hergueta.[26]

*4.2.2. 5-exo,6-exo-5,6-Dibenzoyloxybicyclo[2.2.1]heptane-2,3-dione (**17a**).* Compound **17a** was prepared by the method of Hergueta[26] from the commercially available epimeric mixture of *endo* (~90%) 5-norbornen-2-yl acetate except with an improvement in the step involving selective hydrolysis of the acetate group to produce *exo*,*exo*-5,6-dibenzoyloxybicyclo[2.2.1]-heptan-2-ol (mixture of 2-*endo* and 2-*exo*). Concentrated (32%) HCl (7.5 mL) was added to a solution of (5-*exo*,6-*exo*)-5,6-dibenzoyloxybicyclo[2.2.1]-hept-2-yl acetate (mixture of 2-*endo* and 2-*exo*)[26] (9.35 g, 23.7 mmol) in MeOH (330 mL), and the mixture was stirred at room temperature for 3 d. The reaction mixture was then diluted with EtOAc (600 mL) and poured into aqueous saturated $NaHCO_3$ solution. The EtOAc phase was washed with water and then dried over $MgSO_4$. The organic solvents were removed in vacuo, and the residue was purified by silica gel column chromatography using hexane/EtOAc (1:1 v/v) as eluent, which afforded the alcohol mixture *exo*,*exo*-5,6-dibenzoyloxybicyclo[2.2.1]-heptan-2-ol (mixture of 2-*endo* and 2-*exo*) (7.40 g, 89%) as a waxy solid (*endo*/*exo*-2-hydroxy ratio 4:1), as determined by ^1H NMR. The spectroscopic and physical data was identical to that reported.[26]

4.2.3. exo-2-Oxobicyclo[2.2.1]heptan-6-yl benzoate and exo-2-oxobicyclo[2.2.1]heptan-5-yl benzoate. Under an atmosphere of argon a 1 M solution of borane THF complex (33 mL) was added dropwise to a stirred solution of commercial *endo* (~90%) -5-norbornen-2-yl acetate (9.14 g, 60.1 mmol) dissolved in THF (30 mL) while the reaction mixture was cooled to 0 °C. After 4.5 h at 0 °C, the excess of borane was decomposed by the addition of C_2H_5OH (30 mL). A solution of 30% H_2O_2 (46.2 mL) in saturated aqueous $NaHCO_3$ (110 mL) was then added dropwise over a period of 20 min at 0 °C. The temperature was maintained for an additional 30 min, before being neutralized with 1 M HCl (to pH=6) at 0 °C. The reaction mixture was extracted 3× with diethyl ether and the ethereal extracts were combined, washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo and the resultant residue purified by column chromatography on silica, eluting with toluene/ethyl acetate 4:1 (v/v). The product mixture was predominantly 2-*endo*-6-*exo*-6-hydroxybicyclo[2,2,1]-heptan-2-yl acetate and 2-*endo*-5-*exo*-5-hydroxybicyclo[2,2,1]-heptan-2-yl acetate as a light yellow oil (7.79 g, 77%). The regioisomers were not separated but were used in the next step without further purification. This mixture was reacted with benzoyl chloride according to the method of Sala[27] to give the regioisomeric mixture of 2-*endo*-6-*exo*-6-benzoyloxybicyclo[2,2,1]-heptan-2-yl acetate, 2-*endo*-5-*exo*-5-benzoyloxybicyclo[2,2,1]-heptan-2-yl acetate. Selective acetate hydrolysis was then performed by acid catalysis. Concentrated (32%) HCl (1.2 mL) was added to a MeOH (55 mL) solution of the acetate (1.03 g, 3.76 mmol) and the mixture stirred at room temperature for 3 d. The mixture was diluted with EtOAc (90 mL) and poured into aqueous saturated $NaHCO_3$ solution. The EtOAc phase was washed with brine and then organic solvents was removed in vacuo. CH_2Cl_2 was added to the residue and stirred. The resulting suspension was filtered to remove some insoluble material and then the solvent was evaporated in vacuo to dryness. The resultant residue was purified by silica gel column chromatography, eluting with toluene/ethyl acetate (4:1 v/v) to give the two regioisomers of the alcohols, 2-*exo*-6-*endo*-6-hydroxybicyclo[2,2,1]-heptan-2-yl benzoate and 2-*exo*-5-*endo*-5-hydroxybicyclo[2,2,1]-heptan-2-yl benzoate as a waxy light yellow oils (0.66 g, 76%). The spectroscopic data was identical to that reported except for a small variation in the ratio of the *exo* and *endo* isomers.[27]

This alcohol mixture (8.63 g, 37.2 mmol) dissolved in CH_2Cl_2 (340 mL) was added during 15 min to a stirred, previously prepared mixture of pyridine (37 mL), CH_2Cl_2 (370 mL) and CrO_3 (22.5 g, 225 mmol) kept at 0 °C. After 8 h the mixture was filtered through Celite and the solution evaporated to dryness in vacuo. Purification of the resultant residue by silica gel column chromatography eluting with toluene/ethyl acetate (4:1 v/v) afforded the *title compound* as a colourless solid and a mixture of regioisomers (5.85 g, 68%). Physical properties were identical to those reported.[27]

*4.2.4. exo-2,3-Dioxobicyclo[2.2.1]heptan-5-yl benzoate (**17b**).* The mixture of *exo*-2-oxobicyclo[2.2.1]heptan-6-yl benzoate and *exo*-2-oxobicyclo[2.2.1]heptan-5-yl benzoate from the previous reaction (0.55 g, 2.39 mmol) was added to a mixture of SeO_2 (0.27 g, 2.43 mmol) and xylene (2.6 mL), which was heated under refluxed for 24 h. Selenium metal was removed by filtration through Celite and the solvent removed in vacuo to give a residue that was purified on a column of silica gel, eluting with hexane/EtOAc (1:1 v/v) to afford **17b** as a colourless solid (0.41 g, 70%). An analytical sample was obtained by recrystallization from EtOAc. Mp 182–183 °C. IR (KBr, cm^{-1}): 1714s, 1695m, 1315m, 1273s, 1242s, 1192m, 1107s, 1045m, 966w, 700s. ^1H NMR (DMSO-d_6) δ: 7.97 (2H, d, J=7.2 Hz, 2′, 6′-*Bz*), 7.69–7.65 (1H, t, J=7.6 Hz, 4′-*Bz*), 7.55–7.51 (2H, t, J=7.6 Hz,

3′,5′-*Bz*), 5.49–5.45 (1H, m, 5-*endo*-*H*), 3.06–2.99 (2H, m, 6-*endo*-*H*, 6-*exo*-*H*), 2.41–2.33 (1H, m, 7-*H*), 2.23–2.16 (1H, m, 1-*H*), 2.06–1.99 (1H, m, 4-*H*), 1.98–1.89 (1H, m, 7-*H*). ^{13}C NMR (DMSO-d_6) δ: 175.6, 174.3, 165.2, 133.5, 129.6, 129.3, 128.8, 77.8, 49.7, 41.5, 35.4, 31.3. ESMS (%): *m*/*z* 283 ([M+K$^+$] 100), 245 ([M+H$^+$] 45). Anal. Calcd for $C_{14}H_{12}O_4$ (244.24) C 68.85, H 4.95. Found: C 68.69, H 4.86.

4.2.5. 2-exo,3-exo-Bicyclo[2.2.1]heptane-2,3-diol. A solution of norbornene (5.00 g, 53.1 mmol) was prepared in a mixture of acetone/water (115 mL, 4:1) at 40 °C. To this solution *N*-methylmorpholine *N*-oxide (6.86 g, 58.5 mmol) was added, followed by (after 5 min) a commercial solution of OsO_4 (1.6 mL, 4 wt % in water). The reaction was monitored by TLC and after 21 h the reaction was deemed complete. The acetone was removed in vacuo and the remaining aqueous solution extracted with EtOAc (2×100 mL). The extracts were washed with brine, dried ($MgSO_4$) and solvent removed in vacuo to give the *title compound* as a solid (6.09 g, 89.4%). Data comparable to that reported.[33] ^{1}H NMR ($CDCl_3$) δ: 3.65 (2H, s, *endo*-2,3-*H*), 2.11 (2H, s), 1.73 (1H, d, *J*=10 Hz, CH_2), 1.43 (2H, d, *J*=8.4 Hz, CH_2), 1.07 (1H, d, *J*=10 Hz, CH_2), 1.02 (2H, d, *J*=8.4 Hz, CH_2). ^{13}C NMR ($CDCl_3$) δ: 75.00, 43.26, 31.77, 24.69.

*4.2.6. Bicyclo[2.2.1]heptane-2,3-dione (**17c**).* Dry DMSO (10.8 mL) was added very slowly to a solution of dry trifluoroacetic anhydride (18.9 mL, 135.5 mmol) in dry CH_2Cl_2 (80 mL) at −78 °C, and the mixture was stirred for 10 min. 2-*endo*,3-*endo*-Bicyclo[2.2.1]heptane-2,3-diol (6.09 g, 47.5 mmol) in CH_2Cl_2 (23 mL) was added and the reaction mixture stirred at −78 °C for 5.5 h. After cooling to −100 °C, dry Et_3N (35.4 mL) was added to a well-stirred solution. The temperature was maintained at −78 °C for a further 3 h then allowed to reach 0 °C and left overnight. While still cold the mixture was acidified with 3 M HCl, and then extracted with CH_2Cl_2 (2×120 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and the solvent was removed in vacuo, leaving a dark, viscous oil, which was purified by silica gel column chromatography with EtOAc/Toluene (1:1 v/v) as the eluent, giving **17c** (4.36 g, 74.0%). Consistent with authentic material.[34] ^{1}H NMR ($CDCl_3$) δ: 3.05 (2H, s, *CH*), 2.15–1.99 (4H, m, CH_2), 1.81–1.72 (2H, m, CH_2). ^{13}C NMR ($CDCl_3$) δ: 202, 48.6, 31.8, 24.0.

4.2.7. (1R,2S,3R,4S,5S,6R)-rel-2,3-Diacetate-5,6-dihydroxy-bicyclo[2.2.1]heptane-2,3-dimethanol. A solution of 5-norbornene-2-*exo*-3-*exo*-2,3-dimethanol-2,3-diacetate[35] (3.64 g, 15.3 mmol) A solution of norbornene (5 g, 53.1 mmol) was prepared in a mixture of acetone/water (35 mL, 4:1) at 40 °C. To this solution *N*-methylmorpholine *N*-oxide (1.98 g, 16.8 mmol) was added, followed by (after 5 min) a commercial solution of OsO_4 (460 μL, 4 wt % in water). The reaction was monitored by TLC and after 21 h the reaction was deemed complete. The acetone was removed in vacuo and the remaining aqueous solution extracted with EtOAc (2×100 mL). The extracts were washed with brine, dried ($MgSO_4$) and solvent removed in vacuo to give the *title diol* as a colourless solid (3.95 g, 95%). An analytically pure sample was obtained by recrystallization from EtOAc. Mp 101–102 °C. IR (KBr, cm^{-1}): 3350s, 3235s, 2972s, 2909m, 1736s, 1368s, 1240s, 1111w, 1028s, 980m, 899w, 795w, 606w. ^{1}H NMR ($CDCl_3$) δ: 4.10–4.06 (2H, m, *CH*OAc), 3.96–3.91 (2H, m, C*H*OAc), 3.77 (2H, s, *CH*OH), 2.11 (2H, s, *CH* bridge head), 2.04 (6H, s, *AcO*), 1.90–1.80 (2H, m, *CH*), 1.70 (1H, d, *J*=11.4 Hz, CH_2), 1.40 (1H, d, *J*=11.4 Hz, CH_2). ^{13}C NMR ($CDCl_3$) δ: 170.9, 74.2, 63.3, 46.6, 39.3, 27.2, 21.0. ESMS (%): *m*/*z* 295 ([M+Na$^+$] 100). Anal. Calcd for $C_{13}H_{20}O_6$ (272.29) C 57.34, H 7.40. Found: C 57.50, H7.52.

*4.2.8. (1R,4S,5S,6R)-rel-5,6-Bis[(acetoxy)methyl]bicyclo[2.2.1]heptan-2,3-dione (**17d**).* Using a similar procedure to that described for the synthesis of dione **17c**, the Swern oxidation on (1*R*,2*S*,3*R*,4*S*,5*S*,6*R*)-rel-2,3-diacetate-5,6-dihydroxy-bicyclo[2.2.1]heptane-2,3-dimethanol (3.23 g, 11.9 mmol) gave a crude product that was purified by silica gel chromatography (EtOAc/Toluene, 1:2 v/v) affording the dione **17d** as a yellow glass (2.23 g, 70%). IR (KBr, cm^{-1}): 3447w, 2967w, 1776s, 1759s, 1738s, 1393w, 1369s, 1238s, 1036s, 997m. ^{1}H NMR ($CDCl_3$) δ: 4.28–4.23 (2H, m, *CH*OAc), 4.16–4.10 (2H, m, *CH*OAc), 3.04 (2H, s, *CH*), 2.57–2.49 (2H, m, *CH*), 2.42 (1H, d, *J*=12 Hz, CH_2) 2.08 (6H, s, *AcO*), 2.02 (1H, d, *J*=12 Hz, CH_2). ^{13}C NMR ($CDCl_3$) δ: 200.2, 170.5, 62.0, 52.2, 38.7, 27.1, 20.9. ESMS (%): *m*/*z* 291 ([M+Na$^+$] 100). ESMS HR (TOF) calcd for $C_{13}H_{16}O_6$ [M+Na$^+$] 291.0845. Found: 291.0845.

4.3. General procedure for the urea condensation reactions

The following general methods were used unless otherwise specified.

Method A. Diones **4**, **6**, **11**, **14**, **17a**, **17b**, **17c** and **17d** were all reacted with urea using the following general procedure. Urea (1.20 g, 20.0 mmol) and the dione (10.0 mmol) were suspended in a mixture of TFA (0.3 mL) and benzene (or xylene where specified) (40 mL). This mixture was stirred efficiently for 40 min at room temperature, was then heated under refluxed for 4 h. All water produced during the reaction was removed via a molecular sieve solvent return column. The reaction mixture was then cooled to room temperature and the solvent decanted. A minimum volume of EtOH was added to the residue and the mixture was stirred at room temperature overnight. The colourless solid suspension was collected by filtration, washed with CH_3COCH_3, and air dried for several hours. The products were isolated and analysed as described below.

Method B. The typical reaction conditions involved adding, the diols **18b**, **18c**, or the ureas **13**, **16**, or the dione **11** (0.10 mmol), which were dissolved in a mixture of formamide (3 mL) and TFA (20 μL). Under an atmosphere N_2 the solution was stirred at room temperature for 30 min and then heat to 110–140 °C, as specified for each individual starting material, for a period of 6 h. The reaction mixture was then cooled and the solvent removed in vacuo (0.1 mmHg). A minimal volume of ethanol was added to the remaining residue to isolate a precipitate, which was collected by filtration. The products were isolated and analysed as described below.

Method C. Typically the urea **13** or the diols **18c** and **18d** were suspended in benzene or toluene, while the diones **6**, **11**, **17c** and **17d** were dissolved in either of these solvents. To these mixtures was added urea (2–2.5 mol equiv) and $Bi(OTf)_3$ (5 mol % relative to the starting material [$Bi(OTf)_3$ as a crystalline solid, was prepared according to the method of Antoniotti]).[29] Mixtures were stirred at room temperature for 2 h before heating to reflux (see specific reaction for reaction period). Generated water was removed as describe in *Method A*. At the conclusion of the reaction the mixture was cooled to room temperature and the solvent decanted. The remaining residue was triturated with CH_2Cl_2 twice and the solid obtained was dissolved in a minimal volume of MeOH and the product precipitated by the addition of Et_2O, followed by stirring for 15 min. The solid was then collected by filtration. Some norbornyl derivatives were purified by chromatography as specified below.

*4.3.1. Tetrahydro-3a-(2-acetyloxy-1,1-dimethylethan-1-yl)imidazo[4,5-d]imidazole-2,5(1H,3H)dione (**10b**).* 1-Butyl-2,2-dimethyl-3,4-dioxo acetate (**8**) (1.74 g, 10.1 mmol) was dissolved in THF (3 mL) and added to an acidified (adjusted with HCl to pH=1) solution of urea (1.22 g, 20.3 mmol) dissolved in water (8 mL). The complete mixture was stirred rapidly in a wide mouthed open reaction vessel in order to allow slow evaporation of the solvent. After 5 d at room temperature the resultant solid material was

Please cite this article in press as: Wu, F.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.09.071

collected by filtration and washed thoroughly with methanol and then ether. The methanol and diethyl ether insoluble material was found to be compound **10b** (593 mg, 23%) Mp>260 °C. IR (KBr, cm^{-1}): 3221s, 3170s, 3078m, 1740s, 1678s, 1508w, 1234m, 1122m, 775m. ^1H NMR (DMSO-d_6) δ: 7.31 (2H, s, *NH*), 7.17 (2H, s, *NH*), 5.13 (1H, s, *CH*), 3.84 (2H, s, CH_2), 2.00 (3H, s, *AcO*), 0.89 (6H, s, CH_3). ^{13}C NMR (DMSO-d_6) δ: 170.7, 160.9, 80.5, 68.8, 66.0, 40.4, 21.1, 19.3. ESMS (%): *m/z* 257 ([M+H^+] 74) 279 ([M+Na^+] 84). Anal. Calcd for $C_{10}H_{16}N_4O_4$ (256.16) C 46.8, H 6.3, N 21.9. Found: C 46.7, H 6.7, N 21.5.

The solvent was evaporated from the filtrate and the residue crystallised from methanol to give *6,6-dimethylhexahydro-6a-hydroxy-2H-furo[2,3-d]imidazol-2-one* (**9**) (680 mg, 36%) Mp 216–218 °C. IR (KBr, cm^{-1}): 3317s, 3294s, 3225s, 1705s, 1689s, 1466s, 1223s, 1115s, 1084s, 1042s, 744s. ^1H NMR (DMSO-d_6) δ: 7.31 (1H, s, *NH*), 7.47 (1H, s, *NH*), 6.08 (1H, br s, *OH*), 4.90 (1H, s, *CH*), 3.40 (2H, CH_2O obscured by solvent H_2O), 1.01 (3H, s, CH_3), 0.87 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6) δ: 160.7, 95.6, 91.7, 78.2, 44.3, 22.9, 18.7. ESMS (%): *m/z* 173 ([M+H^+]$^+$ 100) Anal. Calcd for $C_7H_{12}N_2O_3$. 0.15CH_3OH (172.0) C 48.56, H 7.10, N 15.84. Found: C 48.53, H 7.40, N 16.01.

The same products **10b** and **9** were synthesized by stirring a mixture of keto-aldehyde **8** (300 mg, 1.74 mmol), urea (261 mg, 4.35 mmol) and $Bi(OTf)_3$ (5 mol % relative to **8**) in benzene (5 mL) at room temperature for 5 d. The benzene was decanted, the residue washed (3×5 mL) with CH_2Cl_2, then MeOH was added and the products precipitated with diethyl ether. The precipitate was collected by filtration and dried. The dry solid (240 mg) showed only the two products **10b** and **9** in a ratio of 3:2, by ^1H NMR in DMSO-d_6. Compound **10b** (173 mg, 39%) was isolated as a precipitate by dissolving **9** in small volume of dry MeOH. On standing **9** crystallized from the filtrate (46 mg, 17%).

*4.3.2. 7-Methyl-7-(propen-3-yl)-1H,4H-3a,6a-propanoimidazo[4,5-d]imidazole-2,5(3H,6H)dione (**7**).* 3-Methyl-3-(2-propenyl)-1,2-cyclopentadione (**6**) (17.8 mmol) was synthesised from a published procedure[36] for use in *method A* with anhydrous HBF_4 diethyl ether complex as the acid catalyst, in refluxing toluene for 2 h, to give compound **7** (50 mg, 1%) mp>260 °C. IR 3332m, 3224s, 3150s, 1740s, 1684s, 1427m, 1408m, 736s. ^1H NMR (DMSO-d_6) δ: 7.27 (1H, s, *NH*), 7.25 (1H, s, *NH*), 7.21 (1H, s, *NH*), 7.20 (1H, s, *NH*), 5.85–5.71 (1H, m, *CH* double bond), 5.10–4.90 (2H, m, CH_2 double bond), 2.28–1.95 (2H, m, CH_2 ring), 1.95–1.81 (2H, m, CH_2 allylic), 1.62–1.50 (1H, m, CH_2 ring) 1.49–1.38 (1H, m, CH_2 ring), 0.86 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6) δ: 161.5, 161.3, 136.2, 117.9, 86.2, 82.3, 49.1, 38.0, 36.3, 20.4. ESMS (%): *m/z* 237 ([M+H^+] 80) 259 ([M+Na^+] 19). ESMS HR (TOF) calcd ($C_{11}H_{16}N_4O_2$+H^+) 237.1352. Found: 237.1352.

Dione **6** (500 mg, 3.29 mmol) reacted under the conditions of *method C* in toluene (10 mL) for 2 h gave after work-up an off-white solid (510 mg). Recrystallized from MeOH/diethyl ether gave the product **7** as a white solid (310 mg, 40%) identical to the above physical data.

*4.3.3. 4-Methyl-3-oxo-N-cyclopenten-2-yl urea (**5**).* 3-Methyl-1,2-cyclopentadione (**4**) (1.15 g, 11.5 mmol) reacted using *method A* gave compound **5**. Compound **5** was isolated from the reaction mixture after 2 h at reflux, by the removal of the reaction solvent in vacuo and the residue obtained was then purified by silica gel column chromatography eluting with ethyl acetate. Evaporation of the eluting solvent afforded **5** a pale yellow solid (710 mg, 40%). Mp 175 °C. IR (KBr, cm^{-1}): 3412m, 3331m, 3192w, 1682s, 1614s, 1537s, 1371m, 1287m, 1132s, 770m, 638s, 613s. ^1H NMR ($CDCl_3$) δ: 8.10 (1H, s, *NH*), 7.58 (1H, t, *J*=2.8 Hz, *CH* double bond), 5.87–5.08 (2H, br s, NH_2), 2.94–2.82 (1H, m, CH_2 ring), 2.46–2.37 (1H, m, *CH* ring), 2.23 (1H, dt, *J*=18.4 Hz, *J*=2.8 Hz), 1.18 (3H, d, *J*=7.6 Hz, CH_3). ^{13}C NMR ($CDCl_3$) δ: 208.5, 156.5, 138.1, 136.9, 38.5, 34.4, 16.4. ESMS (%): *m/z* 177 ([M+Na]$^+$ 100). Anal. Calcd for $C_7H_{10}N_2O_2$ (154.17) C 54.54, H 6.54, N 18.17. Found: C 54.68, H 6.74, N 18.01.

*4.3.4. (3aS,4R,7S,7aS)-rel-Octahydro-7a-hydroxy-4,7-methano-2-oxo-7,8,8-trimethyl-2H-benzimidazol-3a-yl urea (**13**).* Camphorquinone (**11**) (1.77 g, 10.6 mmol) reacted using *method A* gave compound **13** as a white solid (560 mg, 21%). When **11** (100 mg, 0.68 mmol) was reacted in benzene under the conditions of *method C*, for 2.5 h reflux the yield of **13** was higher (105 mg, 75%). Mp 237 °C. IR (KBr, cm^{-1}): 3325w, 3300w, 1688s, 1657s, 1530m, 1414w, 1364w, 1103s, 824w. ^1H NMR (DMSO-d_6) δ: 7.02 (1H, s, *NH*), 6.63 (1H, s, *NH*), 6.56 (1H, s, *NH*), 6.23 (1H, s, *OH*), 5.88 (2H, s, NH_2), 1.75 (1H, d, *J*=4.0 Hz, *CH* bridge head), 1.51–1.40 (3H, m, CH_2), 1.24–1.17 (1H, m, CH_2), 1.16 (3H, s, CH_3), 0.86 (3H, s, CH_3), 0.79 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6) δ: 159.9, 158.8, 95.9, 79.0, 55.5, 53.6, 47.8, 31.4, 23.0, 22.7, 22.4, 11.3. ESMS (%) *m/z* 269 ([M+H^+] 100) 291 ([M+Na^+] 44). Anal. Calcd for $C_{12}H_{20}N_4O_3 \cdot 0.5H_2O$ (277.32) C 51.97, H 7.63, N 20.20. Found: C 52.14, H 7.59, N 20.00.

*4.3.5. (7S,10R)-rel-1H,4H-7,11,11-Trimethyl-7,10-methano-3a,6a-butanoimidazo[4,5-d]imidazole-2,5(3H,6H)dione (**12**).* Camphorquinone (**11**) (842 mg, 5.10 mmol) reacted in refluxing xylene using *method A* gave compound **12** (190 mg, 15%). Mp>260 °C. IR (KBr, cm^{-1}): 3219m, 3067w, 1730m, 1680s, 1661s, 1487m, 1395m, 1136m, 1109s, 1047m, 779m. ^1H NMR (DMSO-d_6) δ: 7.28 (1H, s, *NH*), 7.20 (1H, s, *NH*), 7.14 (2H, s, *NH*), 1.90 (1H, d, *J*=4.0 Hz, *CH* bridge head), 1.62–1.48 (3H, m, CH_2), 1.34–1.24 (1H, m, CH_2), 1.08 (3H, s, CH_3), 0.94 (3H, s, CH_3), 0.85 (3H, s, CH_3). ^{13}C NMR (DMSO-d_6) δ: 162.2, 160.9, 83.0, 79.6, 52.1, 52.0, 49.3, 30.8, 25.0, 23.1, 20.4, 10.5. ESMS (%) *m/z* 251 ([M+H^+] 100) 273 ([M+Na^+] 8) 501 ([2M+H^+] 40). Anal. Calcd for $C_{12}H_{18}N_4O_2$ (250.30) C 57.58, H 7.25, N 22.38. Found: C 57.40, H 7.41, N 22.37.

The urea **13** (29 mg, 0.11 mmol) reacted further using *method B* at 140 °C for 6 h gave the glycoluril **12** (14 mg, 52%) described above. Using *method C* with refluxing toluene for 24 h the urea **13** (100 mg) affords glycoluril **12** (29 mg, 32%).

Also the camphorquinone (**11**) (500 mg) reacted under the conditions of *method C* in benzene with urea, and refluxed for 20 h, gave the glycoluril **12** (230 mg, 30%).

*4.3.6. (3aS,4R,6S,7R,7aR)-rel-Octahydro-6-acetoyloxy-7a-hydroxy-4,7-methano-2-oxo-2H-benzimidazol-3a-yl urea (**16**). endo/exo* (~9:1) 2.3-dioxobicyclo[2.2.1]heptan-5-yl acetate (**14**) reacted using *method A* gave compound **16** (230 mg, 33%) recrystallised from water. Mp 245–247 °C. IR (KBr, cm^{-1}): 3439w, 3181w, 1728m, 1680m, 1639s, 1526m, 1333w, 1240s, 1159m, 1036m. ^1H NMR (DMSO-d_6) δ: 7.10 (1H, s, *NH*), 6.53 (1H, s, *NH*), 6.35 (1H, s, *OH*), 6.21 (1H, s, *NH*), 5.99 (2H, s, NH_2), 4.92–4.85 (1H, m, *CH*OAc), 2.71–2.68 (1H, m, *CH* bridge head), 2.22 (1H, d, *J*=4.9 Hz, *CH* bridge head), 1.99 (3H, s, *OAc*), 1.96–1.85 (1H, m, CH_2), 1.64–1.54 (2H, m, CH_2 and *CH*), 1.36 (1H, d, *J*=8.0 Hz, *CH*). ^{13}C NMR (DMSO-d_6) δ: 170.9, 160.3, 159.2, 90.8, 74.6, 73.8, 48.9, 46.7, 31.5, 28.4, 21.6. ESMS (%) *m/z* 285 ([M+H^+] 8), 307 ([M+Na^+] 100). Anal. Calcd for $C_{11}H_{16}N_4O_5$ (284.27) C 46.48, H 5.67, N 19.71. Found: C 46.14, H 5.65, N 19.46.

Also isolated from the product mixture was a minor compound **15**. This was obtained by crystallization from water (21 mg, 3%) ^1H NMR (DMSO-d_6) δ: 6.95 (1H, s, *NH*), 6.90 (1H, s, *NH*), 5.39 (1H, s, *OH*), 4.88–4.75 (1H, m, *CH*OAc), 4.65 (1H, s, *OH*), 2.45–2.38 (1H, br obscured by solvent) 2.10 (1H, br s, *CH* bridge head), 1.92 (3H, s, *OAc*), 1.9–1.8 (1H, m, CH_2), 1.78 (1H, d, *J*=8.0 Hz, CH_2), 1.50–1.40 (1H, m, CH_2), 1.31 (1H, d, *J*=8.0 Hz, CH_2). ^{13}C NMR (DMSO-d_6) δ: 170 (obscured by noise see Fig. S9 of Supplementary data), 159.8, 89.8, 89.2, 74.5, 48.6, 46.3, 31.2, 28.5, 21.6.

Please cite this article in press as: Wu, F.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.09.071

*4.3.7. (3aR,4S,5R,6S,7R,7aS)-rel-Octahydro-5,6-dibenzoyloxy-3a,7a-dihydroxy-4,7-methano-2H-benzimidazol-2-one (**18a**). exo,exo*-5,6-Dibenzoyloxybicyclo[2.2.1]heptane-2,3-dione (**17a**) (61 mg, 0.17 mmol) reacted using *method A* gave compound **18a** (17 mg, 24%). Mp 248 °C. IR (KBr, cm^{-1}): 3393s, 3358s, 3069w, 1721s, 1705s, 1686s, 1601w, 1450m, 1404, 1317s, 1287s, 1128s, 1051w, 951w. ^{1}H NMR (DMSO-d_6) δ: 7.75 (4H, d, *J*=8.0 Hz, *Bz*), 7.54 (2H, t, *J*=8.0 Hz, *Bz*), 7.31 (4H, t, *J*=8.0 Hz, *Bz*), 7.27 (2H, s, *NH*), 5.60 (2H, s, *OH*), 5.56 (2H, s, *CH*OBz), 2.45 (2H, s, *CH* bridge head), 2.04 (1H, d, *J*=10.5 Hz, *CH*), 1.63 (1H, d, *J*=10.5 Hz, *CH*). ^{13}C NMR (DMSO-d_6) δ: 164.8, 159.1, 133.4, 129.2, 129.1, 128.5, 87.8, 72.1, 51.9, 28.0. ESMS (%) *m*/*z* 425 ([M+H^+] 37), 447 ([M+Na^+] 100). Anal. Calcd for $C_{22}H_{20}N_2O_7$ (424.41) C 62.26, H 4.75, N 6.60. Found: C 62.50, H 4.76, N 6.48.

*4.3.8. (3aR,4S,5R,7R,7aS)-rel-Octahydro-5-benzoyloxy-3a,7a-dihydroxy-4,7-methano-2H-benzimidazol-2-one (**18b**). exo*-5-Benzoyloxybicyclo[2.2.1]heptane-2,3-dione (**17b**) (86 mg, 0.35 mmol) reacted using *method A* gave compound **18b** (30 mg, 28%). Mp 223–225 °C. IR (KBr, cm^{-1}): 3420s, 3315s, 3015w, 1742s, 1731s, 1432m, 1395m, 1302s, 1270s, 1092m. ^{1}H NMR (DMSO-d_6) δ: 7.94 (2H, d, *J*=8.0 Hz, *Bz*), 7.65 (1H, t, *J*=8.0 Hz, *Bz*), 7.51 (2H, t, *J*=8.0 Hz, *Bz*), 7.10 (1H, s, *NH*), 7.05 (1H, s, *NH*), 5.35 (1H, s, *OH*), 5.26 (1H, d, *J*=6.0 Hz, *CH*OBz), 5.25 (1H, s, *OH*), 2.48–2.42 (1H, m, CH_2), 2.41 (1H, s, *CH*), 2.25 (1H, d, *J*=6.0 Hz, *CH*), 1.60 (1H, d, *J*=10.0 Hz, CH_2), 1.54 (1H, d, *J*=10.0 Hz, CH_2), 1.45–1.35 (1H, m, CH_2). ^{13}C NMR (DMSO-d_6) δ: 165.2, 159.3, 133.3, 130.1, 129.1, 128.8, 88.3, 88.1, 72.8, 52.2, 45.9, 32.9, 29.4. ESMS (%) *m*/*z* 305 ([M+H^+] 100) 327 ([M+Na^+] 13) 609 ([2M+H^+] 47). Anal. Calcd for $C_{15}H_{16}N_2O_5$ (304.3) C 59.21, H 5.30, N 9.21. Found: C 59.19, H 5.33, N 9.28.

17b (300 mg, 1.23 mmol) reacted under the conditions of *method C* and refluxed for 2.5 h gave a residue that was purified by crystallisation from isopropanol/water affording the product **18b** as a light brown solid (305 mg, 82%) identical to above data.

*4.3.9. (3aR,4R,7S,7aS)-rel-Octahydro-3a,7a-dihydroxy-4,7-methano-2H-benzimidazol-2-one (**18c**).* Bicyclo[2.2.1]heptane-2,3-dione (**17c**) (159 mg, 1.28 mmol) reacted using *method A* gave compound **18c** (40 mg, 17%). Mp 216 °C. IR (KBr, cm^{-1}): 3424w, 3296m, 1659s, 1628m, 1470m, 1366m, 1290m, 1136s, 1099s, 773s. ^{1}H NMR (DMSO-d_6) δ: 6.83 (2H, s, *NH*), 5.05 (2H, s, *OH*), 2.10 (2H, s, *CH*), 1.74 (2H, d, *J*=8.0 Hz, CH_2), 1.51 (1H, d, *J*=10.0 Hz, CH_2), 1.26 (2H, d, *J*=8.0 Hz, CH_2), 1.14 (1H, d, *J*=10.0 Hz, CH_2). ^{13}C NMR (DMSO-d_6) δ: 159.6, 89.0, 46.6, 32.3, 22.0. ESMS (%) *m*/*z* 185 ([M+H^+] 100), 207 ([M+Na^+] 53). Anal. Calcd for $C_8H_{12}N_2O_3$ (184.2) C 52.17, H 6.57, N 15.21. Found: C 51.97, H 6.66, N 15.09.

The same product **18c** was synthesized following *method C* where **17c** (100 mg, 0.81 mmol) was dissolved in either benzene or toluene and stirred at room temperature for 2 h over the period of the reaction a pink colour developed. Work-up afforded a light pink solid (126 mg, 85%). The physical data was indiscernible from that described above.

*4.3.10. (7S,10R)-rel-1H,4H-3a,6a-Butano-7,10-methanoimidazo[4,5-d]imidazole-2,5(3H,6H)dione (**20c**).* Bicyclo[2.2.1]heptane-2,3-dione (**17c**) (330 mg, 2.66 mmol) dissolved in toluene was reacted using *method C* where the mixture was finally heated under reflux for 24 h. Following work-up the residue was purified by crystallisation from methanol to afford the urea **19c** as a fine colourless solid (50 mg, 8%). *(3aS,4R,7S,7aS)-rel-Octahydro-7a-hydroxy-4,7-methano-2-oxo-2H-benzimidazol-3a-yl urea* (**19c**). Mp dec 256 °C. IR (KBr, cm^{-1}): 3402m, 3302s, 2962w, 1675s, 1643s, 1605s, 1543m, 1443m, 1381m, 1303w, 1165w, 1103w. ^{1}H NMR (DMSO-d_6) δ: 6.87 (1H, s, *NH*), 6.40 (1H, s, *NH*), 6.27 (1H, s, *NH*), 6.24 (1H, s, *OH*), 5.85 (2H, s, NH_2), 2.39 (1H, s, *CH*), 2.07 (1H, s, *CH*), 1.73–1.54 (2H, m, CH_2), 1.50–1.44 (1H, m, CH_2), 1.39–1.05 (3H, m, CH_2). ^{13}C NMR (DMSO-d_6) δ: 160.3, 159.4, 91.1, 75.9, 47.3, 47.0, 33.0, 23.5, 22.1. ESMS (%) *m*/*z* 227 ([M+H^+] 20), 249 ([M+Na^+] 100), 453 ([2M+H^+] 10), 475 ([2M+Na^+] 60), 701 ([3M+Na^+] 20). ESMS HR (TOF) calcd for ($C_9H_{14}N_4O_3$+H^+) 227.1144. Found: 227.1140.

The solvent was evaporated from the filtrate and the residue purified by chromatography using silica (18–20% methanol in CH_2Cl_2), which gave the product mixed with unreacted urea. Removal of urea by sublimation at 100 °C in vacuo afforded the product **20c** as a colourless powder (25 mg, 5%). Mp>260 °C. IR (KBr, cm^{-1}): 3425m, 3240m, 1740m, 1666s, 1489w, 1381m, 1126w. ^{1}H NMR (DMSO-d_6) δ: 7.15 (2H, s, *NH*), 6.99 (2H, s, *NH*), 2.24 (2H, s, *CH*), 1.69 (1H, d, *J*=12.0 Hz, CH_2), 1.50–1.22 (5H, m, CH_2). ^{13}C NMR (DMSO-d_6) δ: 162.8, 161.2, 80.2, 46.2, 35.5, 23.6. ESMS (%) *m*/*z* 209 ([M+H^+] 85), 231 ([M+Na^+] 87), 439 ([2M+Na^+] 100). ESMS HR (TOF) calcd for ($C_9H_{12}N_4O_2$+H^+) 209.1039. Found: 209.1040; for ($C_9H_{12}N_4O_2$+Na^+) 231.0858. Found: 231.0858.

*4.3.11. (3aR,4S,5R,6S,7R,7aS)-rel-Octahydro-5,6-bis[(acetyloxy)methyl]-3a,7a-dihydroxy-4,7-methano-2H-benzimidazol-2-one (**18d**).* Dione **17d** (268 mg, 1.02 mmol) reacted using *method A* gave compound **18d** as a colourless solid (65 mg, 20%). An analytical sample was obtained by recrystallization from DMF. Mp 236–238 °C. IR (KBr, cm^{-1}): 3431s, 3329s, 1717s, 1383m, 1369m, 1263s, 1248s, 1140m, 1034m, 976w, 905w. ^{1}H NMR (DMSO-d_6) δ: 6.93 (2H, s, *NH*), 5.19 (2H, s, *OH*), 4.06–3.99 (2H, m, CH_2OAc), 3.92–3.84 (2H, m, CH_2OAc), 2.59-2.51 (2H, m, *CH*), 2.03 (2H,s, *CH* bridge head), 1.98 (6H, s, *OAc*), 1.51 (1H, d, *J*=11.5 Hz, CH_2) 1.34 (1H, d, *J*=11.5 Hz, CH_2). ^{13}C NMR (DMSO-d_6) δ: 170.2, 159.3, 88.7, 63.2, 49.9, 35.9, 27.0, 20.8. ESMS (%) *m*/*z* 329 ([M+H^+] 50), 351 ([M+Na^+] 100). ESMS HR (TOF) calcd for ($C_{14}H_{20}N_2O_7$+H^+) 329.1349. Found: 329.1349.

*4.3.12. (7S,8R,9S,10R)-rel-1H,4H-8,9-Bis[(acetyloxy)methyl]-3a,6a-butano-7,10-methano imidazo[4,5-d]imidazole-2,5(3H,6H)dione (**20d**).* The dione (**17d**) (670 mg, 2.56 mmol) dissolved in toluene was reacted using *method C* where the mixture was finally heated under reflux for 40 h. Following the work-up the residue was treated with a minimal volume of cold methanol and a small amount of solid was removed by filtration. The solvent was removed in vacuo and a solid-foam was obtained. Chromatography of this residue on silica eluting with 10% methanol/CH_2Cl_2 gave two main fractions. The least polar fraction gave a glass (94 mg) following evaporation of the solvent. The oxazolidinone **21d** was obtained as an isomeric mixture (oxazolidinone ring *endo* as the major isomer ~73%) following crystallisation from methanol/EtOAc (25 mg, 3%). *1H,4H-8,9-Bis[(acetyloxy)methyl]-3a,6a-butano-7,10-methanooxazolo[4,5-d]imidazole-2,5(3H,6H)dione* (**21d**) Mp 258–260 °C. IR (KBr, cm^{-1}): 3370m, 3248w, 3148w, 1775s, 1736s, 1680s, 1659s, 1427m, 1373m,1250s, 1234s, 1180w, 1134, 1041m, 871w. ^{1}H NMR (DMSO-d_6) δ: 8.80 (1H, s, *NH*), 8.55 (1H, s, *NH* minor isomer), 8.06 (1H, s, *NH* minor isomer), 7.86 (1H, s, *NH*), 7.84 (1H, s, *NH* minor isomer), 7.63 (1H, s, *NH*), 4.19–4.02 (2H, m, CH_2OAc), 4.03–3.82 (2H, m, CH_2OAc), 2.42 (1H, s, *CH*), 2.40 (1H, s, *CH* minor isomer), 2.37 (1H, s, *CH*), 2.36–2.06 (2H, m, *CH*), 1.97 (3H, s, *OAc*), 1.95 (3H, s, *OAc*), 1.93–1.84 (1H, m, CH_2 both isomers), 1.54 (1H, d, *J*=12 Hz, both isomers CH_2). ^{13}C NMR (DMSO-d_6) δ: 173.7, 173.6, 164.0, 162.7, 161.0, 160.1, 101.3, 100.0, 81.7, 80.8, 64.45, 64.40, 64.3, 49.8 (other peaks obscured by solvent), 39.6, 39.4, 39.0, 38.0, 32.1, 21.1, 21.04, 21.0, 20.98. ESMS (%) *m*/*z* 354 ([M+H^+] 88), 376 ([M+Na^+] 100), 707 ([2M+H^+] 65), 729 ([2M+Na^+] 35), 1060 ([3M+H^+] 6), 1082 ([3M+Na^+] 6). ESMS HR (TOF) calcd for ($C_{15}H_{19}N_3O_7$+Na^+) 376.1121. Found: 376.1125.

The second more polar fraction afforded the glycoluril **20d**, also as a glass (59 mg) that was crystallised from methanol/EtOAc (15 mg, 2%). Mp>260 °C. IR (KBr, cm^{-1}): 3441s, 1728s, 1682s, 1381s, 1257m, 1134w, 1033w. ^{1}H NMR (DMSO-d_6) δ: 7.30 (2H, s, *NH*), 7.11 (2H, s, *NH*), 4.15–4.04 (2H, m, CH_2OAc), 3.92–3.80 (2H, m, CH_2OAc), 2.22 (2H, br s, *CH*), 2.19 (2H, s, *CH*), 1.97 (6H, s, *OAc*), 1.76 (1H, d,

J=11.8 Hz, CH_2 bridge), 1.59 (1H, d, J=11.8 Hz, CH_2 bridge). ^{13}C NMR (DMSO-d_6) δ: 170.7, 162.7, 161.4, 80.0, 63.1, 49.4, 38.1, 30.7, 21.3. ESMS (%) m/z 353 ([M+H$^+$] 68), 375 ([M+Na$^+$] 65), 705 [2M+H$^+$] 16), 727 ([2M+Na$^+$] 12). ESMS HR (TOF) calcd for ($C_{15}H_{20}N_4O_6$+H$^+$) 353.1461. Found: 353.1462.

Acknowledgements

This work was supported by the Research Training Scholarship Scheme of UNSW Canberra.

Supplementary data

^{1}H and ^{13}C NMR spectra of purified compounds includes **5**, **7**, **9**, **10b**, **12**, **13**, **15**, **17b**, **17d**, **18a**, **18b**, **18c**, **18d**, **19c**, **20c**, **20d** and **21d**. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.071.

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