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Metal-Catalyzed Cycloisomerization Reactions of *cis*-4-Hydroxy-5-alkynylpyrrolidinones and *cis*-5-Hydroxy-6-alkynylpiperidinones: Synthesis of Furo[3,2-*b*]pyrroles and Furo[3,2-*b*]pyridines

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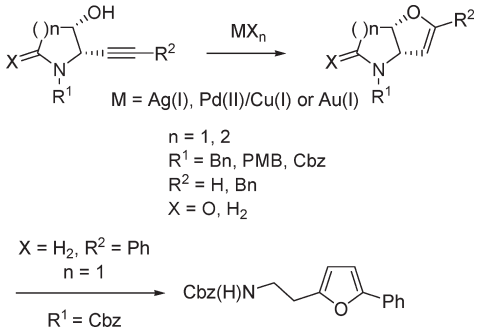

Furo[3,2-*b*]pyrroles and furo[3,2-*b*]pyridines can be conveniently prepared in good yields from the cycloisomerization reactions of *cis*-4-hydroxy-5-alkynylpyrrolidinones and *cis*-5-hydroxy-6-alkynylpiperidinones, respectively, using Ag(I), Pd(II)/Cu(I), or Au(I) catalysis. In one case, the cycloisomerization product was unstable and produced a furan derivative by a ring-opening reaction.

Introduction

The furo[3,2-*b*]pyrrole nucleus **1** (X = O) is a key structural feature of the bioactive fungal metabolites lucilactaene,[1] a cell-cycle inhibitor in p53-transfected cancer cells, 13α-lucilactaene,[2] the structurally related alkaloids fusarins A and D,[3] and the telomerase inhibitors UCS1025A and B (Figure 1).[4] A general and versatile synthesis of this heterocyclic ring system and its furo[3,2-*b*]pyridine homologue **2** would thus provide valuable scaffolds for new drug discovery programs (Scheme 1). Bicyclic heterocyclic systems **1** and **2** could in principle be prepared via a metal-catalyzed cycloisomerization of the heterocyclic *cis*-β-hydroxy alkynes **4** (n = 1, 2) followed by reduction of the resulting unsaturated bicyclic heterocyclic system **3** (Scheme 1).

The synthesis of unsaturated five-membered ring heterocycles in general, via metal-catalyzed cycloisomerization reactions of homopropargylic alcohols, amines (and their N-derivatives), and thiols and related *ortho*-alkynyl phenols, anilines, and arylthiols, is well-established.[5] In the case of homopropargylic alcohols, Pd(II),[6] $(Et_3N)Mo(CO)_5$,[7] Au(I),[8] and Pt(II)[9] have been employed as catalysts in the

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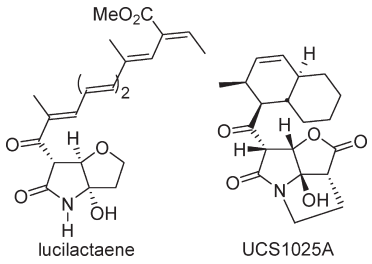
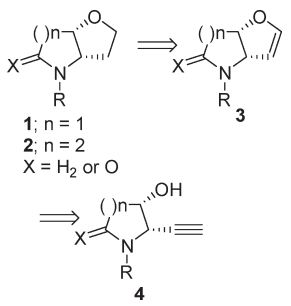


FIGURE 1. Furo[3,2-*b*]pyrrole-based natural products.

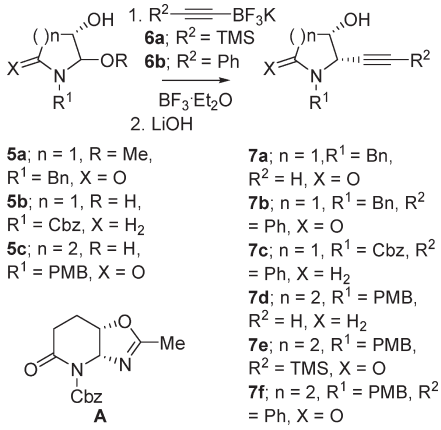
SCHEME 1



key C−O bond forming reaction. Reactions involving the latter two metal catalysts have been performed in alcohol solvent, resulting in conversion of the initially formed 1,2-dihydrofuran to a 2-alkoxytetrahydrofuran.[8,9] In the case of homopropargylic alcohol itself, cycloisomerization with Ag_2CO_3 was not successful and only starting material was recovered.[10] Bis-homopropargylic alcohols (4-alkyn-1-ols) undergo cycloisomerization reactions with Pd(II),[6] Ag(I),[11] Au(I),[8,12] Pt(II),[9] Ir(I),[13] Ru(I),[14] and $(Et_3N)Mo(CO)_5$,[15] to give 5-*exo*[7,9,11−13] and/or 6-*endo*[14,15] cyclic enol ether products. 5-Alkyn-1-ols often give 6-*exo* products;[9,12,13] however, under $(Et_3N)Mo(CO)_5$ catalysis, seven-membered ring glycals have been formed.[15] While the cycloisomerization reactions of acyclic homopropargylic alcohols are well-documented, we are not aware of such studies on saturated cyclic *cis*-*β*-hydroxy alkynes, either carbocyclic (2-alkynyl-1-cycloalkanols) or heterocyclic analogues related to **4**, to give bicyclic systems incorporating a dihydrofuran moiety. The lack of ready accessibility of these cyclic *cis*-*β*-hydroxy alkyne substrates may be a major reason for this.

We report here a direct method for the synthesis of the novel heterocyclic *cis*-hydroxy alkynes **7a**−**c**, via *cis*-diastereoselective reactions of cyclic *N*-acyliminium ions[16] with potassium 1-alkynyltrifluoroborates and the synthesis of novel furo[3,2-*b*]pyrrole and furo[3,2-*b*]pyridine derivatives from the metal-promoted cycloisomerization of these substrates under Ag(I), Pd(II)/Cu(I), or Au(I) catalysis.

SCHEME 2



Results and Discussion

The *cis*-hydroxy alkyne substrates **7a**−**c** were prepared via the $BF_3 \cdot Et_2O$-catalyzed reactions between the hemiaminals **5a**−**c**[17,18] and the potassium alkynyltrifluoroborates **6a**,**b** (Scheme 2 and Table 1). We[17] and Batey et al.[18] have previously reported the successful reactions of **5b**,**c** with vinyl and arylboronic acids. Under similar reaction conditions that we have developed earlier,[17] the reactions of 1-benzyl-4*S*-hydroxy-5-methoxypyrrolidin-2-one **5a** with the potassium 1-alkynyltrifluoroborates **6a**,**b** gave the 4,5-*cis*-adducts **7a** and **7b**, respectively, with high *cis*-diastereoselectivity and in moderate to good yields, respectively (Table 1, entries 1 and 2). In contrast, the reaction of racemic *N*-Cbz-4,5-dihydroxypyrrolidine **5b** with **6b** gave the racemic hydroxy alkyne **7c** in 89% yield as a 73:27 mixture of diastereomeric adducts that could be separated (Table 1, entry 3).

The six-membered ring hemiaminal (5*S*)-**5c** gave the corresponding 5,6-*cis*-adducts **7d**, **7e**, and **7f** with high diastereoselectivity but in modest yields (Table 1, entries 4−6). These yields were low due to formation of the known Ritter reaction product **A**, comprising 18−30% of the product yields, formed between the in situ generated cyclic *N*-acyliminium ion and acetonitrile.[19] The use of alternative solvents such as nitromethane did not improve the yields of **7d**−**f**. To assist in the stereochemical assignments of these adducts, these reactions were repeated on the 4-*O*- and 5-*O*-protected analogues **8a**−**c** of the substrates **5a**−**c**, respectively (Scheme 3). The reactions were highly *trans*-diastereoselective and proceeded in generally higher yields (Table 2). This was due in part to the better solubility properties of the substrates in the nonparticipating solvent dichloromethane.

The 4,5-*cis*-stereochemistry of products **7a** and **7b** was based on the magnitude of $J_{4,5}$ (5.0 and 5.1 Hz, respectively) for these compounds. Their related *trans*-isomers **9a** (R^3 = Ac, Bn, and TBPDS) and *trans*-**7b** that was prepared from *O*-TBS deprotection of **9c** (Supporting Information) had $J_{4,5}$ values of 0−2 Hz. In related literature examples, $J_{4,5}$

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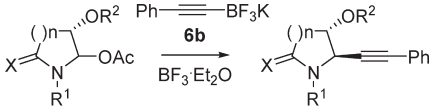
TABLE 1. Synthesis of *cis*-β-Hydroxy alkynes 7a−f

entry	substrate	boronate	temp (°C) /time (h)	solvent	product (yield (%))	*cis*/*trans*
1	**5a**	**6a**	0/1 then rt/12	$MeNO_2$	**7a**[a] (41)	95:5
2	**5a**	**6b**	0/1 then rt/4	MeCN	**7b** (70)	100:0
3	**5b**	**6b**	0/2	MeCN	**7c** (89)	73:27
4	**5c**	**6a**	0/1 then rt/16	MeCN	**7d**[a] (31)[b]	100:0
5	**5c**	**6a**	0/1 then rt/16	MeCN	**7d** (33) **7e**[c] (4)	100:0
6	**5c**	**6b**	0/1 then rt/16	MeCN	**7f** (36)[b]	91:9

[a] After treatment of the reaction mixture with aqueous LiOH solution, rt, 1 h. [b] The known Ritter reaction product **A**[19] was also isolated (entry 4, 18% and entry 6, 30%). [c] This reaction did not include treatment with LiOH, consequently compound **7e** was isolated along with the major product **7d**.

SCHEME 3



8a; n = 1, R^1 = Bn, R^2 = Ac, X = O
8b; n = 1, R^1 = Bn, R^2 = Bn, X = O
8c; n = 1, R^1 = Bn, R^2 = TBDPS, X = O
8d; n = 1, R^1 = Cbz, R^2 = Ac, X = H_2
8e; n = 2, R^1= PMB, R^2 = Ac, X = O

9a; n = 1, R^1 = Bn, R^2 = Ac, X = O
9b; n = 1, R^1 = Bn, R^2 = Bn, X = O
9c; n = 1, R^1 = Bn, R^2 = TBDPS, X = O
9d; n = 1, R^1 = Cbz, R^2 = Ac, X = H_2
9e; n = 2, R^1= PMB, R^2 = Ac, X = O

TABLE 2. Synthesis of *trans*-β-Hydroxy alkynes 9a−e

entry	substrate	temp (°C)/time (h)	solvent	product (yield (%))	*trans*/*cis*[a]
1	**8a**	0/1 then rt/12	CH_2Cl_2	**9a** (68)[b]	90:10
2	**8b**	0/1 then rt/12	CH_2Cl_2	**9b** (89)	100:0
3	**8c**	0/1 then rt/12	CH_2Cl_2	**9c** (71)	100:0
4	**8d**	0/1 then rt/16	CH_2Cl_2	**9d** (77)	100:0
5	**8e**	0/1 then rt/16	CH_3CN	**9e** (86)	84:16

[a] Ratio from ^{1}H NMR analysis of crude reaction mixture. [b] Ratio of *trans*/*cis* = 96:4 after purification by column chromatography.

is typically 0−2.5 Hz for *trans*-isomers and 6.0−7.5 Hz for the corresponding *cis*-isomers.[17] For compound **9d**, $J_{4,5}$ was < 1 Hz, consistent with its relative 4,5-*trans*-configuration; however, $J_{4,5}$ for its corresponding *cis*-isomer, **7d**, could not be determined due to peak broadening. The *cis*-stereochemistry of **7e** was established by a single-crystal X-ray analysis (see Supporting Information).

The $BF_3 \cdot Et_2O$-catalyzed reactions between *N*-benzyl-3,4,5-triacetoxy-2-pyrrolidinone and potassium 1-alkynyltrifluoroborates have previously been shown to be 4,5-*cis*-diastereoselective (4,5-*cis*/4,5-*trans* = 70−90:30−10).[20] The stereochemical outcomes of these reactions, however, were thought to be due to neighboring group participation of the 3-acetoxy group; this group is absent in our substrate **5a**. The *cis*-diastereoselectivity observed in the products **7a**−**c**, therefore, arises via a different reaction mechanism, presumably via a boronate intermediate involving the free hydroxyl group of substrates **5a**−**c**.[17]

Initial studies on the cycloisomerization reactions of the *cis*-β-hydroxy alkynes **7a**−**e** involved their reactions with $AgNO_3$,[21] $Au(Ph_3P)Cl$,[8a,b] or $PdCl_2(Ph_3P)_2$/CuI,[22] using modified literature procedures. Consequently, compounds **7b** and **7f** (both bearing a phenyl alkynyl moiety) were cycloisomerized into the corresponding dihydrofurans **10b** and **10e** in good to excellent yields using all three of the chosen catalyst systems in DMF as solvent (Table 3, entries 2−5 and 14−16). While substrates **7b** and **7f** required reaction temperatures of 60−70 °C, the substrate **7c** underwent reaction at rt with all three catalysts in DMF (not shown in Table 1) or MeOH (Table 1, entries 6−8). These reactions gave not the expected product **10c** but the furan derivative **11** (Scheme 4). The structure of **11** was clear from NMR analysis that showed resonances for two vicinally coupled furan methines (δ_H 6.54 (d, J = 3.5 Hz), δ_c 105.7 (H-4/C-4), and δ_H 6.13 (*d*, J = 3.5 Hz), δ_c 108.7 (H-3/C-3)) and a carbamate NH (δ_H 4.99−4.87 (br s)). This compound clearly arises from a ring-opening reaction of the desired product **10c**, surprisingly at rt and in the absence of a strong base or acid catalyst. Notably, the *N*-Boc analogue of **10c**, but lacking the 5-phenyl substituent, is a known compound that was stable to distillation at low pressure.[23]

It was also observed that 30 mol % of AgF (DMF, 65−70 °C, 2.5 h) and Ag_2O (MeOH, rt, 5 h) could be used in the silver-catalyzed reactions of **7b** (70% yield of **10b**) and **7c** (77% yield of **11**), respectively. Compounds **7a** and **7d**, each bearing a terminal alkyne, were cycloisomerized using $AgNO_3$ to their respective dihydrofurans **10a** and **10d** (Table 3, entries 1 and 9); however, all attempts to cycloisomerize compound **7d** using either the Au(I) or Pd(II)/Cu(I) catalyst systems were unsuccessful, leading only to the recovery of the starting material. The $AgNO_3$-mediated cyclization of compound **7e**, bearing the trimethylsilylethynyl moiety, led to the formation of **10d**, with the associated loss of the TMS group (Table 3, entry 10). The order of catalyst reactivity in these reactions proved to be $AgNO_3$ > $PdCl_2(Ph_3P)_2$/CuI>$Au(Ph_3P)Cl$. Catalyst loadings of $PdCl_2(Ph_3P)_2$ were low (4 mol %), while the higher loading used for $Au(Ph_3P)Cl$ (10−30 mol %) reflected the slower observed rates of reaction when using this catalyst. $AgNO_3$ and $Au(Ph_3P)Cl$ could be used in amounts as low as 5−10 mol % (Table 3, entry 11 and footnotes a−c); however, this resulted in slower reaction times and slightly decreased yields. The corresponding *trans*-β-hydroxyl alkyne **9** (n = 1, R^2 = H, X = O) did not undergo a cycloisomerization reaction with any of the aforementioned catalysts.

In order to further explore the synthetic potential of metal-catalyzed cycloisomerizations of *cis*-β-hydroxy alkynes of the type **7**, the sequential palladium-catalyzed cycloisomerization/cross-coupling reactions of **7b**,**c** were examined

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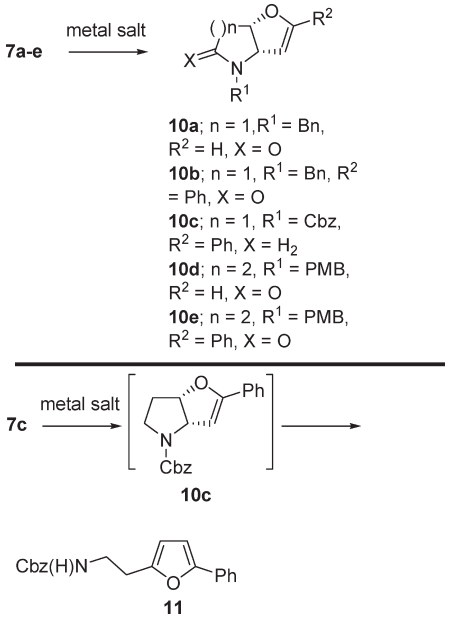
TABLE 3. Cycloisomerization Reactions of Substrates 7a−f

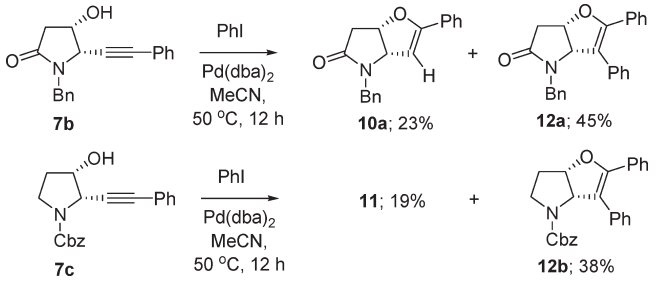
entry	substrate	catalyst (mol %)	temp (°C)	time (h)	solvent	product (yield (%))
1	**7a**	$AgNO_3$ (26)	65−70	1.5	DMF	**10a** (68)
2	**7b**	$AgNO_3$ (12)	65−70	1.5	DMF	**10b** (77)
3	**7b**	$Au(Ph_3P)Cl$ (22)	65−70	24	EtOH	**10b** (72)
5	**7b**	$PdCl_2(Ph_3P)_2$ (4) CuI (10)	65−70	1.5	DMF	**10b** (70)
6	**7c**	$AgNO_3$ (25)[a]	rt	2	MeOH	**11** (82)
7	**7c**	$Au(Ph_3P)Cl$ (30)[b]	rt	8	MeOH	**11** (87)
8	**7c**	$PdCl_2(Ph_3P)_2$ (4) CuI (5)	rt	8	MeOH	**11** (69)
9	**7d**	$AgNO_3$ (10)[c]	60−65	4	DMF	**10d** (60)
10	**7e**	$AgNO_3$ (22)	60 then rt	2 then 16	DMF	**10d** (66)
11	**7f**	$AgNO_3$ (18)	60−65	4	DMF	**10e** (75)
12	**7f**	$Au(Ph_3P)Cl$ (17)	60−65	5 d	EtOH	**10e** (79)
13	**7f**	$PdCl_2(Ph_3P)_2$ (4) CuI (7)	60−65	16	DMF	**10e** (63)

[a] 10 mol % of $AgNO_3$ (rt, 10 h) gave 75% of **11**. [b] 10 mol % of $Au(Ph_3P)Cl$ (rt, 21 h) gave 74% of **11**. [c] 5 mol % of $AgNO_3$ (60−65 °C, 8 h) gave 54% of **10d**.

SCHEME 4



SCHEME 5



using iodobenzene.[24] These reactions gave moderate yields of the arylated products **12a** (45%) and **12b** (38%), respectively, along with significant amounts of the previously observed products **10b** (23%) and **11** (19%), respectively (Scheme 5). We assume that compound **10b** arises via protonation of a 3-PhPd(II)-furo[3,2-*b*]pyrrole intermediate, while products **12a**,**b** are from reductive elimination of this same or analogous Pd(II) complex, respectively. Interestingly, compound **12b** was stable under the reaction conditions and did not produce the corresponding ring-opened furan derivative.

In conclusion, furo[3,2-*b*]pyrroles and furo[3,2-*b*]pyridines can be conveniently prepared in good yields from the cycloisomerization reactions of *cis*-4-hydroxy-5-alkynylpyrrolidinones and *cis*-5-hydroxy-6-alkynylpiperidinones, respectively, using Ag(I), Pd(II)/Cu(I), or Au(I) catalysis. The *N*-Cbz substrate **7c** gave an unexpected furan product (**11**). These β-hydroxy alkyne substrates are readily prepared from the $BF_3 \cdot Et_2O$-catalyzed reactions between in situ formed *N*-acyliminium ions and potassium 1-alkynyltrifluoroborates. $AgNO_3$ proved to be the most effective catalyst for these cycloisomerization reactions in terms of substrate versatility, rate of reaction, and catalyst loading (down to 5−10 mol %).

Experimental Section

(4*S*,5*S*)-1-Benzyl-5-ethynyl-4-hydroxypyrrolidin-2-one (7a). To a stirred solution of **5a** (60 mg, 0.27 mmol) and potassium trimethylsilylacetylenetrifluoroborate **6b**[25] (166 mg, 0.81 mmol) in $MeNO_2$ (1.3 mL) maintained at 0 °C under a nitrogen atmosphere was added $BF_3 \cdot Et_2O$ (0.154 g, 1.08 mmol). The resulting mixture was stirred for 1 h before warming to rt and stirring for a further 12 h. The reaction mixture was then diluted with EtOAc (8 mL) and washed with $NaHCO_3$ (8 mL of a 10% aqueous solution). The separated organic phase was dried then concentrated under reduced pressure. The resulting residue was dissolved in THF (5 mL) then treated with LiOH (2 mL of a saturated aqueous solution), and the resulting mixture was stirred for 1 h before being diluted with EtOAc (8 mL). The separated organic layer was dried and the solvent removed in vacuo. The resulting crude product (present only as the *cis*-diastereomer, as judged by ^1H NMR analysis) was purified by column chromatography (silica, 2:1 v/v EtOAc/petrol + 0.5% MeOH). Concentration of the relevant fractions (R_f 0.5 in 2:1 v/v EtOAc/petrol + 0.5% MeOH) gave the title compound **7a** (24 mg, 41%) as a pale yellow solid: mp 74−76 °C; $[\alpha]_D^{25}$ −17.1 (*c* 2.1, $CHCl_3$); υ_{max} 3314, 2929, 2371, 1673, 1439, 1414, 1291, 1072, and 708 cm^{-1}; δ_H 7.33−7.27 (5H, complex m), 5.10 (1H, d, J = 14.7 Hz), 4.37 (1H, m), 4.23 (1H, dd, J = 2.0 and 5.0 Hz), 4.02 (1H, d, J = 14.9 Hz), 2.64 (1H, dd, J = 17.1 and 6.6 Hz), 2.63 (1H, d, J = 2.0 Hz), 2.51 (1H, dd, J = 17.1 and 3.5 Hz); δ_C 172.0, 136.0, 128.7, 128.4, 127.8, 78.1, 76.3,

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65.4, 55.3, 44.4, 39.1; MS (ESI^+) m/z 216 [$(MH)^+$, 100%]; HRMS (ESI^+) found 216.1018, $C_{13}H_{14}NO_2$ requires $(MH)^+$, 216.1025.

(4*S*,5*R*)-1-Benzyl-4-(acetyloxy)-5-(phenylethynyl)pyrrolidin-2-one (9a). To a stirred solution of **8a**[3] (100 mg, 0.34 mmol) and potassium phenylacetylenetrifluoroborate **6b** (92 mg, 0.44 mmol) in CH_2Cl_2 (1.5 mL) maintained at 0 °C under a nitrogen atmosphere was added dropwise $BF_3 \cdot Et_2O$ (0.20 g, 1.37 mmol). The resulting mixture was stirred for 1 h before being warmed to rt and stirred for a further 12 h. The reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (8 mL of a saturated aqueous solution). The separated organic layer was dried and then concentrated under reduced pressure. The crude product (90:10 ratio of *trans*/*cis*) was purified by column chromatography (silica, 1:3 v/v EtOAc/petrol), and concentration of the relevant fractions (R_f 0.55 in 1:3 EtOAc/petrol) afforded the title compound **9a** (78 mg, 68%, 96:4 *trans*/*cis* mixture) as a light brown gum: $[\alpha]_D^{22}$ −65.3 (*c* 3.0, $CHCl_3$); υ_{max} 1744, 1700, 1490, 1408, 1231, 1036, and 703 cm^{-1}; δ_H (major *trans*-diastereomer) 7.40−7.26 (10H, complex m), 5.34 (1H, d, J = 6.5 Hz), 5.14 (1H, d, J = 15.2 Hz), 4.27 (1H, s), 4.11 (1H, d, J = 15.2 Hz), 3.05 (1H, dd, J = 17.9 and 6.6 Hz), 2.53 (1H, d, J = 17.9 Hz), 2.03 (3H, s); minor *cis*-diastereomer 7.40−7.26 (10H, complex m), 5.90 (1H, s), 5.06 (d, J = 15.0 Hz), 4.17 (1H, s), 4.15 (1H, d, J = 15.0 Hz), 2.80 (1H, dd, J = 17.0 and 7.0 Hz), 2.70 (1H, dd, J = 17.0 and 2.5 Hz); δ_C (major *trans*-diastereomer) 171.4, 170.0, 135.5, 131.8, 128.9, 128.7, 128.3, 128.2, 127.7, 121.6, 87.2, 82.4, 72.0, 55.5, 44.5, 36.9, 20.8; MS (ESI^+) m/z 334 [$(MH)^+$, 100%]; HRMS (ESI^+) found 334.1450, $C_{21}H_{20}NO_3$ requires $(MH)^+$, 334.1443.

(3a*S*,6a*S*)-4-Benzyl-2-phenyl-6,6a-dihydro-3a*H*-furo[3,2-*b*]pyrrol-5(4*H*)-one (10b). Method A ($AgNO_3$): A magnetically stirred solution of **7b** (30 mg, 0.10 mmol) in DMF (1 mL) maintained at rt under a nitrogen atmosphere was treated with $AgNO_3$ (2 mg, 0.012 mmol). The reaction mixture was then heated at 65−70 °C for 1.5 h, before being cooled and diluted with water (3 mL). The resulting mixture was extracted with EtOAc (2 × 10 mL). The combined extracts were dried, and the solvent was removed in vacuo. The crude product was subjected to column chromatography (silica, 1:4 v/v EtOAc/petrol), and concentration of the relevant fractions (R_f 0.5 in 1:4 v/v EtOAc/petrol) gave the title compound **10b** (23 mg, 77%) as a colorless gum: $[\alpha]_D^{24}$ −9.3 (*c* 1.6, $CHCl_3$); υ_{max} 1669, 1438, 1248, 1020, and 756 cm^{-1}; δ_H 7.53−7.28 (10H, complex m), 5.38 (1H, d, J = 2.4 Hz), 5.17 (1H, app t, J = 7 Hz), 4.92 (1H, d, J = 14.8 Hz), 4.71 (1H, dd, J = 7.8, 2.2 Hz), 4.07 (1H, d, J = 14.8 Hz), 2.97 (1H, dd, J = 18.0 and 7.1 Hz), 2.88 (1H, d, J = 18.0 Hz); δ_C 171.7, 160.4, 136.2, 129.6, 129.5, 128.7, 128.4, 128.3, 127.7, 125.7, 93.5, 77.4, 65.5, 44.7, 38.3 MS (ESI^+) m/z 292 [$(MH)^+$, 100%]; HRMS (ESI^+) found 292.1356, $C_{19}H_{18}NO_2$ requires $(MH)^+$, 292.1338.

Method B ($Pd(PPh_3)_2Cl_2$/CuI): To a stirred solution of **7b** (30 mg, 0.10 mmol) in DMF (1 mL) maintained at rt under a nitrogen atmosphere were added $Pd(PPh_3)_2Cl_2$ (3 mg, 4.0 μmol) and CuI (2 mg, 0.01 mmol). The resulting mixture was heated at 65−70 °C for 1.5 h, before being cooled and diluted with water (3 mL). The resulting mixture was extracted, and the crude product was subjected to column chromatography as described above to give the title compound **10b** (21 mg, 70%) as a colorless gum. The spectral data of the purified product were in good agreement with those obtained from the sample of compound **10b** prepared by Method A.

Method C ($Au(PPh_3)Cl$): To a stirred solution of **7b** (10 mg, 0.046 mmol) in EtOH (0.6 mL) maintained at rt under a nitrogen atmosphere was added $Au(PPh_3)Cl$ (5 mg, 0.01 mmol). The resulting mixture was heated at 65−70 °C for 24 h before being cooled and diluted with water (2 mL). The resulting mixture was extracted, and the crude product was subjected to column chromatography as described above to give the title compound **10b** (7 mg, 72%) as a colorless gum. The spectral data of the purified product were in good agreement with those obtained from the sample of compound **10b** prepared by Method A.

(3a*S*,6a*S*)-4-Benzyl-2,3-diphenyl-6,6a-dihydro-3a*H*-furo[3,2-*b*]pyrrol-5(4*H*)-one (12a). A solution of iodobenzene (49 mg, 0.24 mmol) and K_2CO_3 (66 mg, 0.48 mmol) in acetonitrile (1.5 mL) maintained at 50 °C under a nitrogen atmosphere was treated with $Pd(dba)_2$ (7 mg, 7.2 μmol). The resulting mixture was stirred for 30 min before adding a solution of **7b** (35 mg, 0.12 mmol) in acetonitrile (1.5 mL), and stirring was continued for a further 12 h. The reaction solvent was then removed in vacuo, and the resulting residue was filtered through a short plug of silica gel using EtOAc. The filtrate was concentrated under reduced pressure, and the resulting crude material was purified using flash column chromatography (1:3 v/v EtOAc/petrol) to furnish three fractions, A, B, and C. Concentration of the fraction A (R_f 0.5 in 1:4 v/v EtOAc/petrol) gave compound **10b** (8 mg, 23%) as a colorless gum. The spectroscopic data of this material were in good agreement with those obtained from the sample of compound **10b** prepared previously. Concentration of the fraction B (R_f 0.5 in 1:3 v/v EtOAc/petrol) gave compound **12a** (20 mg, 45%) as a white solid: mp 144−146 °C; $[\alpha]_D^{23}$ +44.0 (*c* 1.0, $CHCl_3$); υ_{max} 1682, 1433, 1227, 911, and 765 cm^{-1}; δ_H 7.36−6.73 (15H, complex m), 5.21−5.17 (1H, m), 5.13 (1H, d, J = 7.8 Hz), 4.96 (1H, d, J = 15.2 Hz), 3.40 (1H, d, J = 15.2 Hz), 3.04−2.96 (2H, m); δ_C 172.4, 154.1, 135.9, 134.0, 130.3, 129.2, 129.1, 128.9, 128.4, 128.1, 127.95, 127.5, 127.4, 127.3, 111.0, 75.8, 68.5, 44.5, 38.2; MS (ESI^+) m/z 368 [$(M+H)^+$, 100%]; HRMS (EI^+) found 367.1572, $C_{25}H_{21}NO_2$ requires M^+, 367.1565. Concentration of fraction C (R_f 0.5 in 2:1 v/v EtOAc/petrol + 1% MeOH) gave unreacted **7b** (10 mg) as a colorless solid.

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Supporting Information Available: General experimental procedures and full experimental procedures and characterization data as well as copies of the ^1H NMR and ^{13}C NMR spectra of all new compounds. Crystal/refinement data and ORTEP plot of compound **7e** (CCDC 724111). This material is available free of charge via the Internet at http://pubs.acs.org.