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Strategy for the Construction of Lactones via Ene-reaction

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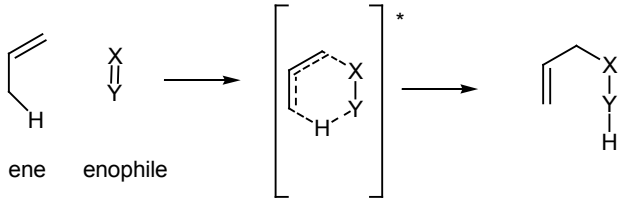
Abstract An effective ene-reaction protocol was developed for the preparation of cis-fused bicyclic lactones catalyzed by various Lewis acids at low temperatures.

Keywords Ene-reaction, Lactones, Lewis acid, Low temperature

1. Introduction

The synthesis of the *cis*-fused bicyclic lactones relies extensively on the Lewis acid catalysed carbonyl-ene reaction which has been widely used to access carbocycles.[1] In 1943 Alder discovered the ene-reaction and classified it in his Nobel Lecture as an “indirect substitution addition” or “ene synthesis" in 1950. The synthesis of the bicyclic lactone intermediate relies on the intramolecular ene reaction, a conversion that has been widely used as a tool to access polycycles. The conversion involves the reaction between an alkene having an allylic hydrogen (an"ene") and a compound containing an electron deficient double bond (an "enophile") to form a σ-bond with migration of the ene double bond and a 1,5-hydrogen shift Scheme 1.0 [1]



Scheme 1.0

As part of a programme aimed at the rapid and efficient synthesis of complex iridoid natural products, we reported efficient and novel process of a precursor **(216)** via ene reaction. Scheme 1.1

2. Results & Discussion

The synthesis on a suitable scale of the key bicyclic lactone **(216)** would require an efficient and robust synthesis of the precursor **(127)**. Initial inspection of the intermediate **(127)** suggests that it could be conveniently assembled by coupling the C-5 cabanion of 3-methyl-2(5H)-furanone **(214)** with the terminal cation of 4-bromobutene in a 1,4 addition protocol. Once this is achieved, subsequent modification is required, which involves the cleavage of the 1,3-dioxalane to aldehyde and a further ene-reaction protocol would afford bicyclic lactone **(216)**. Unfortunately, the behaviour of 2-furanolate ions is inconsistent. Pattenden [2] has observed that the lithium enolate obtained from 3-methyl-2(5H)-furanone **(214)** on alkylation with various ally bromides gives both C-3 and C-5 substitutions. It was envisaged that C-5 regioselectivity could be induced by recourse to the 2-(trialkylsiloxy) furan, which behaves as the equivalent of the localized C-5 of the 2(5H)-furanone entity **(214)**. Protection of the carbonyl group of 3-methyl-2-(5H)-furanone **(214)** was achieved following the procedure reported by Jefford. [3] It was envisaged that compound **(215)** could conveniently furnish compound **(127)** with high regioselectivity. The possibility that **(215)** could be converted to **(127)** was considered on the basis of a report by Jefford[3] that ω-bromogeranyl acetate could undergo alkylation at C-5 position of siloxyfurans to furnish the corresponding butenolides in good yields. This model compound was considered to explore the efficacy of this transformation. It was envisaged that activation with silver salt could provide the desired selectivity. Having the essential reagents in hand, the next step was set out to put them together to create the precursor **(127)**. The coupling was achieved with a stiochiometric amount of silver trifluoroacetate and, in keeping with previous findings of Jefford, alkylation occurred with high regioselectivity. Unfortunately in our systems the yield was found to be 9% for, when 4-bromobutene was used as the coupling agent. In an attempt to establish optimized conditions for this reaction, it was discovered the yield could be greatly increased to 69% for **(127)**, when the temperature was kept at -78°C during the addition of 4-iodobutene **(238)** Scheme 1.2.

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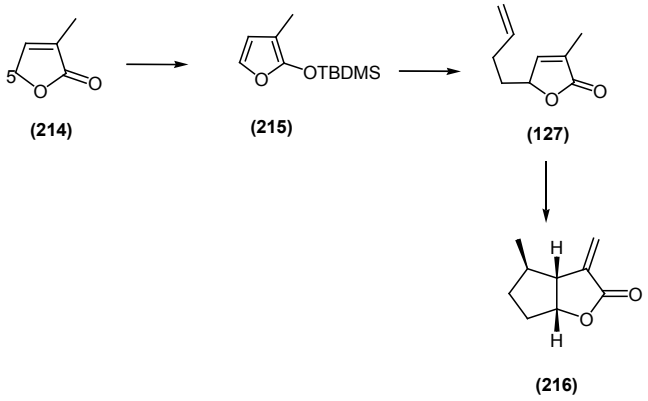
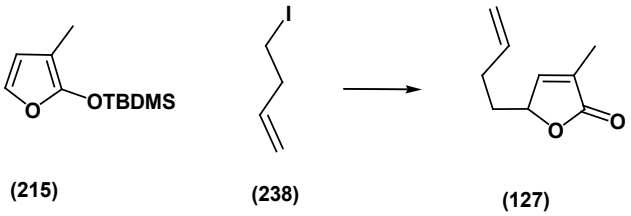


Scheme 1.1



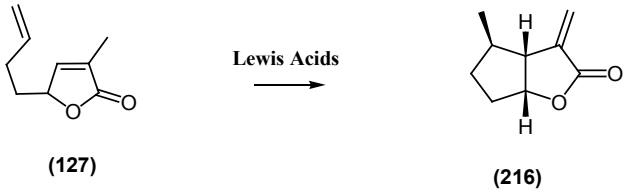
(a) silver trifluoroacetate, DCM -78°C, 69%

Scheme 1.2

3. Lewis Acid Catalyze Carbonyl Ene-reaction

The attempted synthesis of the *cis*-fused bicyclic lactone **(216)** and **(217)** was to involve the reactions of **(127)** using an ene-reaction using procedure reported by Snider. [4] According to this method, Me_2AlCl was added to solutions of **(127)** in DCM at -78°C under nitrogen and the resulting mixtures were allowed to warm to room temperature with stirring for 48 hours. After workup, ^1H NMR analysis revealed that **(216)** and **(217)** have been formed. The protocol was repeated with different Lewis acids to isolate the *endo*-diastreoisomer (216) in good yield. The stereochemical assignment of -*cis* at ring junction and the *endo* methyl group were achieved via nOe.

Table 1. Lewis Acid catalyzed ene reaction of precursor (127)



Entry	Reagents	Solvent	Yield/% (**216**)
1	$BF_3.OEt_2$	DCM	78
2	$BF_3.OEt_2$	THF	72
3	$AlCl_3$	DCM	74
3	$MgBr.OEt_2$	THF	82
4	Me_2AlCl	DCM	61

3-methyl 2-(*tert*-butyldimethylsiloxy) furan (215)

To a stirred solution of 3-methyl-2-(5H)-furanone **(214)** (1.00 g, 10.2 mmol, 1.00 equiv), triethylamine (1.36 g, 13.22 mmol, 1.29 equiv.), and dry ether (7.5 mL) under an atmosphere of nitrogen at 0°C was added via syringe, *tert*-butyldimethylsilyl triflate (3.23 g, 13.0 mmol, 1.27 equiv). After 3 hours water (10 mL) was added, the organic layer was separated, the residue was extracted with diethyl ether (3 x 7.5 mL). The ether layer was washed with cold aqueous saturated sodium hydrogen carbonate (2 x 5 mL). The solvents were removed *in vacuo* and the residue was purified by flash column chromatography on silica, eluting with hexane: ether (5:1) to furnish the title compound as a colourless oil (1.66 g, 77%); υ_{max} (thin film/cm^{-1}), 2999, 2956, 2887, 2865, 1656, 1261, 956, 851; δ_H (250 MHz, $CDCl_3$) 6.69 (1H, d, *J* 2.2 Hz, C**H**O), 6.04 (1H, d, *J* 2.2 Hz, C**H**CHO), 1.79 (3H, s, C**H$_3$**), 0.95 (9H, s, t-butyl), 0.23 (6H, s, dimethyl); δc (62.5 MHz, $CDCl_3$) 153.2, 131.5, 113.9, 92.5, 26.1, 26.0, 18.5, 8.83, -2.55, -4.6; $^m/_z$ (C.I) 213 (MH^+, 33%), 212 (100%), 181 (17%), 169 (4.9%), 130 (8.8%), $C_{11}H_{21}SiO_2$, requires 213.1312, found 213.1316.

5-(But-3-enyl)-3-methylfuran-2(5H)-one (127)

Method A

To a stirred suspension of silver trifluoroacetate (395 mg, 1.8 mmol, 1.13 equiv) in dry dichloromethane (10 mL) under argon at -78°C was added 2-*tert*-butyldimethylsiloxy)-methylfuran **(215)** (350 mg, 1.6 mmol, 1.00 equiv) followed by the dropwise addition of 4-boromo-but-1-ene **(237)** (220 mg, 16 mmol, 1.00 equiv) neat over a period of 5 minutes. The temperature was increased to 10°C over 4 h. The mixture was filtered through Celite®, washing with ether (4 x 4 mL). The solvent was removed carefully *in vacuo* and the crude material was purified by flash column chromatography on silica, eluting with hexane: ether (4:1) to furnish the title compound as a pale yellow oil (22 mg, 9%); ν_{max} (thin film) 3019, 2924, 1751, 1646, 1446, 1423, 928; δ_H (250 MHz, $CDCl_3$) 6.96 (1H, m, C**H**=C), 5.70 (1H, dt, J_{trans} 17.1, J_{cis} 10.3, *J* 6.8, C**H**=CH_2), 4.99-4.89 (2H, m, C**H$_2$**=CH), 4.83-4.80 (1H, m, C**HO**), 2.15 (2H, bq, *J* 7.9 Hz, C**H$_2$**CH_2CHO), 1.81 (3H s, C**H$_3$**C=C), 1.73-1.61 (2 H, m C**H$_2$**CHO); δ_C (62.5 MHz, $CDCl_3$) 174.6, 149.0, 137.1, 130.3, 116.3, 80.8, 33.1, 31.8, 30.1; $^m/_z$ (C.I) 152 (MH^+, 1.3%), 130 (100%), 118 (70%), $C_9H_{13}O_2$, requires 153.0909, found 153.0924.

Method B

To a stirred suspension of silver trifluoroacetate (3.50 g, 15.8 mmol, 1.32 equiv.) in dry dichloromethane (32 mL) under argon at -78°C was added 2-(*tert*-butyldimethylsiloxy)-methylfuran **(215)** (2.54 g, 12 mmol, 1.00 equiv.) followed by the dropwise addition of 4-iodobut-1ene **(238)** (2.85 g, 15.70 mmol, 1.3 equiv.) neat over a period of 10 minutes. The temperature was increased to 10°C over 4 h. The mixture was filtered through Celite®, washing with ether (4 x 32 mL). The solvent was removed carefully *in vacuo* and the crude material was purified by

flash column chromatography on silica, eluting with hexane: ether (4:1) to furnish the title compound as a pale yellow oil (1.26 g, 69%).

4-methyl-3methylene-hexahydrocyclopenta[b]furan-2-one 216

To a stirred a solution of 5-(But-3-enyl)-3-methylfuran-2(5H)-one **(127)** (200 mg, 1.31 mmol, 1 equiv) in dry dichloromethane (7 mL) under argon -78°C was added BF_3 (115 mg, 1.7 mmol, 1.3 equiv) and reaction was stirred for 24 h by which time TLC analysis revealed the formation of a new product. Water (10 mL) was added and the organic layer separated, the residue was extracted with DCM (4 x 10 mL). The DCM layer was washed with cold aqueous saturated sodium hydrogen carbonate (2 x 4 mL). The solvents were removed *in vacuo* and the residue was purified by flash column chromatography on silica, eluting with hexane : ethyl acetate (1:1) to furnish **(216)** as a colourless oil (156 mg, 78%); (thin film/cm^{-1}), 2933, 1751, 1644, 1442, 1430, 922; δ_H (400 MHz, $CDCl_3$) 6.18 (1H, bs, C**H$_2$**=CH), 5.62 (1H, bs, C**H$_2$**CH), 4.16 (1H, q, *J* 5.4 Hz, *J* 2.2 Hz, **CH**O), 2.76 (1H, dd, *J* 5.6 Hz, *J* 1.9 Hz, **CH**CHO), 1.91-1.60 (3H, m, **CH$_2$**CHO, **CH**CH_3), 1.59-1.53 (1H, m, **CH$_2$**$CHCH_3$), 1.35-1.1.30 (1H, m, **CH$_2$**$CHCH_3$), 1.08 (3H, d, *J* 6.6 Hz, **CH$_3$**); δ_C (100 MHz, $CDCl_3$) 174.3, 133.1, 120.3, 88.4, 53.4, 41.5, 31.5, 29.4, 17.7; $^m/_z$ (C.I) 153 (MH^+, 100%), $C_9H_{12}O_2$, requires 153.0916, found 153.0914.

4. Conclusions

Our proposed synthetic approach to the bicyclic lactone system systems using the ene-reaction a novel method was successful and gave the correctly placed lactones. It was deduced that it may be successful due to the Lewis acid complexing with the furan alkene, therefore, lowering the energy of the LUMO which affects the HOMO-LUMO interaction and allowed the cyclization protocol.

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