THE SYNTHESSES OF (R)-(+)−β-VANILLYL-γ-BUTYROLACTONE
AND OF CHIRAL LIGNANS THEREFROM

Eric Brown* and Alain Daugan
Laboratoire de Synthèse Totale de Produits Naturels (UA n°482), Faculté des Sciences, Route de Laval, BP 535, 72017 Le Mans, France

Abstract - (R)-(+)−β-vanillyl-γ-butyrolactone was obtained in 4 steps including a resolution, from vanillin and dimethyl succinate, and was used for the total syntheses of 5 naturally occurring and optically active lignans such as (+)-isolariciresinol 20.

We recently described efficient syntheses of the (R)-(+) and (S)-(−)-lactones 1 and 2, which are key-intermediates for biologically active chiral lignan derivatives.1 We now describe here the synthesis of the hitherto unknown (R)-(+)−β-vanillyl-γ-butyrolactone 3 which we used for the syntheses of naturally occurring, and optically active lignans.

A Stobbe condensation between vanillin and dimethyl succinate could be carried out without preliminary protection of the phenolic hydroxyl, when using methanolic lithium methoxide (2.6 equ.) as a base. The resulting ethylenic half-ester 4, mp 142-144°C (MeOH), was thus obtained in 90% yield. When the same reaction was carried out by means of sodium methoxide, the yield of the half-ester 4 was 20% only. Catalytic hydrogenation (H2, Pd-C, AcOH) of the latter gave the racemic half-ester 5, mp 91-93°C (85% yield) which was next treated with 1 equ. (R)-(+)−α-methylbenzylamine in AcOEt. The least soluble salt was purified by recrystallization giving fine needles, mp 126-134°C, [α]D +28° (c 1, CHCl3) (74% yield). Treatment of this salt with aqueous HCl nearly quantitatively afforded the pure half-ester (R)-(+)−5, mp 97.5-100.5°C (Et2O) and [α]D +29° (c 1.2, MeOH). Recrystallization of the more soluble salt gave big macles, mp 104-108°C, [α]D -12° (c 1.2, CHCl3) and in 68% yield. Acidic treatment of the latter gave the half-ester (S)-(−)−5, mp 98-101°C and [α]D -29° (c 1.1, MeOH).

Reduction of the potassium salt of the half-ester (R)-(+)− was carried out in EtOH for 4 days at room temperature (RT) using a tenfold excess of Ca(BH4)2 as the reducing agent,2 thus affording the desired β-vanillyl-γ-butyrolactone (R)-(+)−3 in 83% yield, mp 119.5-121.5°C (CH2Cl2/Et2O) and [α]D +10° (c 1, CHCl3). The half-ester (S)-(−)−5 similarly yielded the lactone (S)-(−)−3, mp 119-121°C and [α]D −10° (CHCl3).
Syringaldhyde was \( \text{O} \)-benzylated using benzyl chloride (EtOH/KI/K\(_2\)CO\(_3\), 6 h reflux, 90% yield) and subsequent NaBH\(_4\) reduction of the aldehydic carbonyl quantitatively afforded the alcohol \( 7 \), mp 47-49°C (Et\(_2\)O/petroleum ether) which was described as an oil.\(^3\) Treatment of the latter with PBr\(_3\) in ether quantitatively yielded the hitherto unknown and unstable bromide \( 8 \), mp 40-42°C. Since our preliminary attempts failed to alkylate the lactone \( (R)-(+)\)-3 at C-2 using the bromide \( 8 \) and 2.2 equ. of LDA as a base, we therefore decided to protect the phenolic hydroxyl of \( (R)-(+)\)-3 by means of benzyl chloride (2 equ.) in a similar way as above (Me\(_2\)CO, 16 h). The resulting compound \( (R)-(+)\)-6 was thus obtained in 90% yield, mp 80-81.5°C and \([\alpha]_D\) \(+4^o\) (CHCl\(_3\)).

The lithium anion of the lactone \( (R)-(+)\)-6 was generated using LDA in THF and was treated with the bromide \( 8 \) for 3 h at -80°C, thus giving the amorphous compound \( 9 \), \([\alpha]_D\) \(-20^o\) (c 1, CHCl\(_3\)), in 78% yield after chromatography. The benzyl groups of \( 9 \) were cleaved by catalytic hydrogenolysis (H\(_2\), \( 3^\text{bars}, \text{Pd-C, AcOEt}, 15 \text{h} \)) and \((-)\)-thujaplicatin methyl ether \( 10 \) was thus obtained in 78% yield, having mp 168-168.5°C (Me\(_2\)CO/H\(_2\)O) and \([\alpha]_D\) \(-44^o\) (c 1.1, Me\(_2\)CO), after recrystallization from Me\(_2\)CO/H\(_2\)O. The literature\(^4\) indicates mp 167-167.5°C and \([\alpha]_D\) \(-48.7^o\) (c 4, Me\(_2\)CO).

Formation of the lithium anion of the lactone \( (R)-(+)\)-6, using lithium hexamethyldisilamid (LHDS) in THF at -80°C, followed by slow addition of the known bromide \( 11^5 \) gave \( \text{O} \)-dibenzylmatairesinol \( 12 \) as a viscous colourless oil in 87% yield after chromatography, having \([\alpha]_D\) \(-22^o\) (c 1, CHCl\(_3\)). When this alkylation reaction was carried out using LDA instead of LHDS, the resulting compound \( 12 \) thus obtained was contaminated with an impurity of same Rf, presumably a dialkylated product. The fact that the use of LHDS may lead to a purer alkylation product was recently disclosed in the literature.\(^6\) Catalytic hydrogenation (H\(_2\), Pd-C, AcOEt) of the benzyl groups of \( 12 \) gave natural \((-)\)-matairesinol \( 13 \) in 80% yield after chromatography, mp 70-72°C (EtOH/H\(_2\)O) and \([\alpha]_D\) \(-43^o\) (c 0.84, Me\(_2\)CO). The literature\(^7\) indicates mp 117-119°C (CHCl\(_3\)) and \([\alpha]_D\) \(-42.8^o\) (Me\(_2\)CO).

LiAlH\(_4\) reduction in THF at RT of the lactone ring of compound \( 12 \) gave the diol \( 14 \), mp 113-114.5°C, \([\alpha]_D\) \(-24^o\) (c 0.9, CHCl\(_3\)) in 66% yield. Catalytic hydrogenolysis (H\(_2\), Pd-C, AcOEt) of the benzyl groups of \( 14 \) afforded natural \((-)\)-secoisolariciresinol \( 15 \) in 76% yield, mp 112-113.5°C, \([\alpha]_D\) \(-32^o\) (c 0.8, Me\(_2\)CO). The literature\(^8\) indicates mp 112-114°C, \([\alpha]_D\) \(-32^o\) (Me\(_2\)CO). The diol \( 15 \) was dehydrated and cyclized by means of HClO\(_4\) in refluxing acetone for 20 min, thus leading to natural \((-)\)-anhydrosecoisolariciresinol \( 16 \), mp 120.5-121.5°C, \([\alpha]_D\) \(-62^o\) (c 0.5, EtOH) in 74% yield after chromatography. The literature indicates mp 118-118.5°C and \([\alpha]_D\) \(-58^o\) (EtOH).

The lactone \( (R)-(+)\)-6 was next hydroxyalkylated with \( \text{O} \)-benzylvanillin using LHDS in benzene at 0°C for 5 min, giving the amorphous mixture of epimeric carbinols \( 17 \) in 87% yield after chromatography. The intramolecular cyclization of alcohols \( 17 \) by means of trifluoroacetic acid in the usual way, or by means of H\(_2\)SO\(_4\), afforded mixtures containing partially debenzyalted products. However the mixture of alcohols \( 17 \) was intramolecularly cyclized in a neat fashion using 60% aqueous perchloric
(R)-(+): H-3a; (S)-(-): H-3b
1. R, R' = CH₂
2. R = R' = Me
3. R = Me; R' = H
4. R = Me; R' = Bz

(R)-(+): H-2a
(S)-(-): H-2b
7. X = OH, R = Me
8. X = Br, R = Me
11. X = Br, R = H

4 → (R,S)-5 → (R)-(+)-5 → (R)-(+)-3 → (R)-(+)-6
(R)-(+)-6 + 8 → 9 → 10
(R)-(+)-6 + 11 → 12 → 13 → 14 → 15

17
18
19 R = Bz
20 R = H
acid in AcOH/CH₂Cl₂ for 4 h 30 min at RT, thus affording D-dibenzylretrodendrin 18, mp 178-180°C (CH₂Cl₂/MeOH), [α]₀D -63° (c 1.15, CHCl₃) and in 78% yield after chromatography. LiAlH₄ reduction of the lactone ring of 18 in THF at RT for 1 h gave D-dibenzylisolariciresinol 19, mp 122-123.5°C (AcOEt/Et₂O), [α]₀D +1° (c 1, CHCl₃), and in 80% yield after chromatography. ¹H-NMR (CDCl₃), δ (ppm): 7.7-7.2 (10H, m), 6.9 (1H, d), 6.7 (3H, m), 6.3 (1H, s), 5.16 (2H, s), 4.86 (2H, s), 3.83 (3H, s), 3.71 (3H, s), 3.66 (1H, m), 3.5 (2H, d), 3.36 (2H, d), 2.96-2.6 (4H, m), 2.15-1.56 (2H, m). Finally, catalytic hydrogenolysis (H₂, 3 atm., Pd-C, AcOEt, RT, 18 h) of the benzyl groups of 19 furnished natural (+)-isolariciresinol 20, mp 149-151°C (CHCl₃), [α]₀D +68° (c 0.84, Me₂CO) and in 81% yield after chromatography. The literature indicates mp 155-157°C (CHCl₃/MeOH) and [α]₀D +68° (c 1, Me₂CO).

All the compounds described in this paper were characterized by IR and ¹H-NMR spectroscopy. The twelve new compounds (R)-3, (S)-3, 4, (R,S)-5, (R)-5, (S)-5, (R)-6, 9, 12, 14, 18 and 19 also gave good microanalytical results.

Conclusion

The present work confirms the fact that resolution of α-benzylhemisuccinic esters can provide an efficient and easy access to natural lignans and their enantiomers. By this method, in the present work as well as in previous ones,¹ we were able to obtain in a preparative fashion eighteen optically active lignoids, including ten natural lignans.

REFERENCES

   b) ibid., 1986, 27, 3719.

Received, 15th December, 1986