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A TOTAL SYNTHESIS OF C-NOR D-HOMOSTEROIDS OF THE A → B → C → D TYPE, INVOLVING A REDUCTIVE ALKYLATION STEP FOR CONSTRUCTION OF THE D-RING

Eric BROWN* and Jacques LEBRETON

Laboratoire de Synthèse Totale de Produits Naturels (U.A. n° 482),
Faculté des Sciences, Route de Laval, BP 535, 72017 Le Mans, France.

Summary : A stereospecific total synthesis of the racemic C-nor D-homosteroid compound 14, which has six asymmetric carbons and which presents the natural trans-anti-trans configuration, was carried out in twelve steps starting from the Wieland-Miescher ketone 1.

In 1978, we described a total synthesis of C-nor D-homosteroïds following a novel pathway of the A → B → C → D type, as the result of a chemical work originated in the early seventies.[1,2] Since that time, considerable progress has been reported in the literature concerning alkylation and annelation reactions, as well as protecting group methodology. We therefore decided to reinvestigate the total synthesis of C-nor D-homosteroids following a similar strategy, but using recent reaction methodology whenever possible.

Thus, we describe here a stereospecific total synthesis of the C-nor D-homosteroid compound 14 with six asymmetric carbons. Reaction of the Wieland-Miescher ketone 1 with 2,2-dimethylpropanediol in the presence of Et_2O-BF_3 afforded the required ketal 2 as the major product and in 60-80% yields, having m.p. 104-105°C, lit.[3] m.p. 96°C. Indeed, 2,2-dimethylpropanediol was found to be definitely superior to ethylene glycol for carbonyl protection in the present synthesis. Birch reduction of the ethylenic ketone 2, using twice distilled dry ammonia and 99,9% pure lithium, gave the trans decalone 3 in 85-100% yields after purification by chromatography. The yield of this reduction was markedly lower, when less pure ammonia and lithium were used. Compound 3 has m.p. 91,5-92,5°C but has been described as an oil.[3]

Reduction of the carbonyl group of 3 using L-selectride in THF at -78°C selectively gave the axial alcohol 4 (72% yield), m.p. 57-60°C. Hydrolysis of the 1,3-dioxane group of 4, using concentrated HCl in acetone at 0°C, yielded the ketol 5,[4] m.p. 112-113°C (75-80%). Protection of the hydroxy group of 5 by means of methoxyethoxymethyl chloride (MEM-Cl), in the presence of diisopropylethylamine in CH_2Cl_2 at 0°C, gave the compound 6 as a colourless oil in 90% yield after purification by chromatography.

At this stage, various methods for α-acetonylation of ketones were systematically tried, using either the ketone 6 or similar decalones as substrates. For instance, the lithium enolate of 6 (generated with LDA), was treated with either 3-bromo-2-methoxypropene[5]

or 3-chloro-2-trimethylsiloxypropene,[6] under a variety of experimental conditions, but this failed to give the expected γ-diketone 9 after hydrolysis of the corresponding reaction products. Reaction of the lithium derivative of the hydrazone 7 (*vide infra*) with 3-chloro-2-trimethylsiloxypropene again met with no success. Alkylation of the lithium enolate of 6 with methallyl chloride invariably gave a mixture of mono and dialkylated products, from which the desired monomethallyl compound was found very difficult to isolate in a pure enough state.

Finally, in our hands, an acceptable α-acetonylation method of the ketone 6 was carried out using Corey's hydrazone alkylation sequence.[7] Reaction of 6 with N,N-dimethylhydrazine at 110°C afforded the corresponding oily hydrazone 7 (85%). The latter was treated with n-butyllithium and the resulting carbanion was quenched with methallyl chloride, giving the α-alkylated intermediate 8 (oil, 70-80%). A selective transformation of the hydrazone group of 8 into the starting carbonyl could not be accomplished satisfactorily by the standard procedures involving either copper acetate in THF, or the OsO_4/KIO_4 or $KMnO_4/KIO_4$ couples.

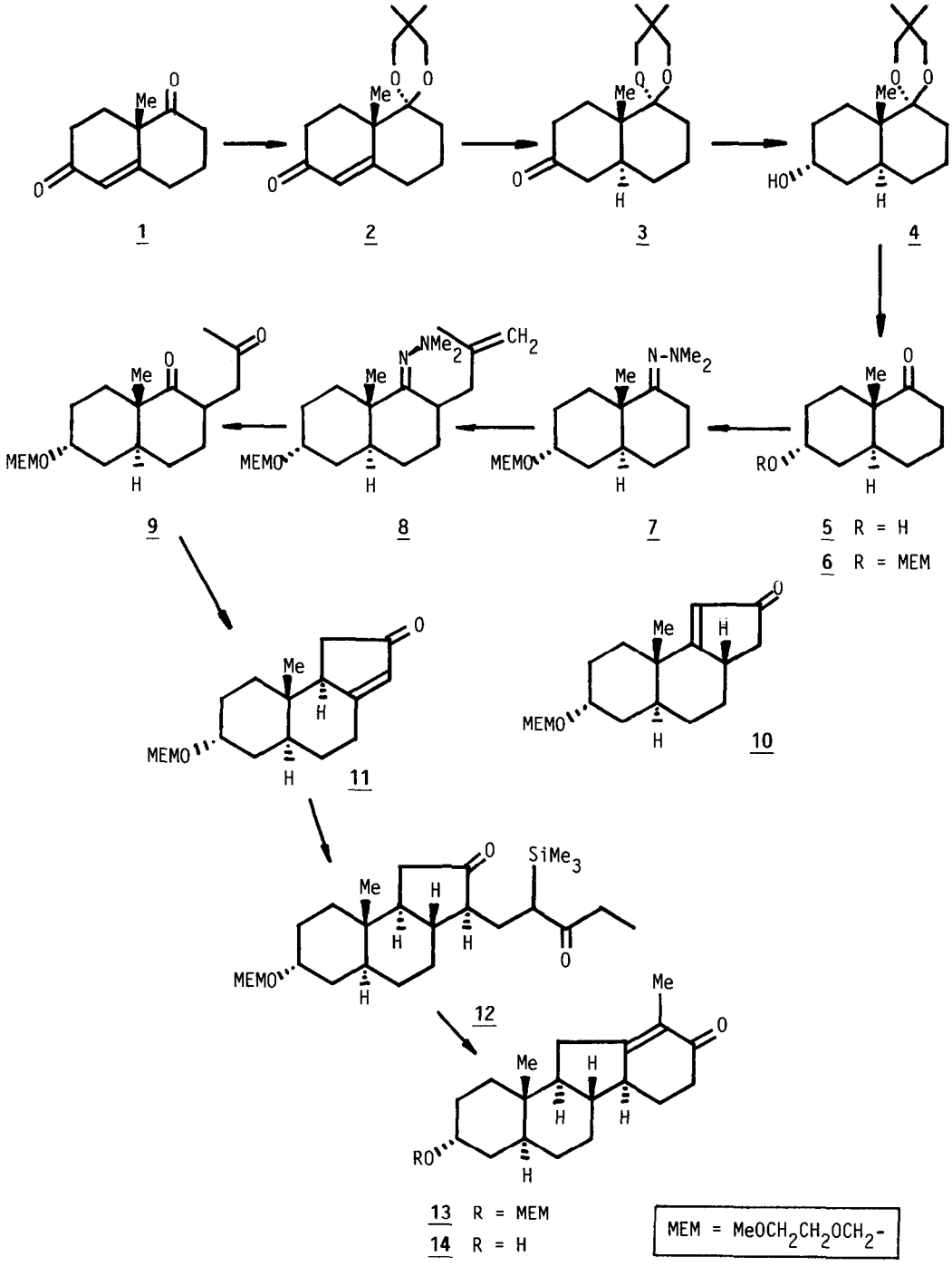
Therefore, compound 8 was ozonolyzed in CH_2Cl_2 at -78°C and after reduction of the intermediate ozonide with Zn/AcOH, the required γ-diketone 9 was obtained in 40-50% yields after chromatography as a colourless oil which darkened rapidly.

Intramolecular crotonisation of the γ-diketone 9, using t-BuONa (5 eq.) in benzene at room temperature for 3 hours,[8] gave a mixture of benzindenones 10 and 11 in the ratio ca. 3:1 and in 60-75% yields. The compound 11 clearly resulted from the migration of the double bond of 10. The angular methyl group appeared at δ 1.14 ppm and δ 0.64 ppm in the ^1H NMR spectra of 10 and 11, respectively. Since 10 and 11 proved difficult to separate, other cyclization methods liable to lead to a single compound were next investigated. No reaction was observed when the γ-diketone 9 was treated with LDA in THF, or with lithium hexamethyldisilazide in benzene, under a variety of experimental conditions.

On the other hand, and contrary to previous findings,[9,10] intramolecular crotonisation of the γ-diketone 9, using NaH in a refluxing benzene solution containing a trace of tertio-amyl alcohol,[9] did not afford the expected benzindenone 10. Instead, the isomeric enone 11 was obtained as the sole product in 68% yields after chromatography.

Construction of the D-ring could now be carried out on the enone 11 in the desired fashion, by using a reductive alkylation procedure.[11,12] Thus, the double bond of the enone 11 was reduced with lithium in liquid ammonia under the same conditions as above, and the resulting carbanion was trapped with ethyl trimethylsilylvinyl ketone, giving the intermediate 12, which was identified by its IR spectrum and was not further purified and characterized. The crude δ-diketone 12 was next desilylated and cyclized using KOH in methanol, giving the tetracyclic compound 13.

We could not remove the hydroxyl protecting group of 13 by means of the standard procedure using excess $ZnBr_2$ in CH_2Cl_2 at room temperature. However, hydrolysis of compound


1
2
3
4
5 R = H
6 R = MEM
7
8
9
10
11
12
13 R = MEM
14 R = H
MEM = MeOCH2CH2OCH2-

13, with concentrated HCl in acetone at 0°C, followed by chromatography and recrystallization from ether, gave pure C-nor D-homosteroid compound 14, m.p. 154-155°C in 35% overall yield from the enone 11. The structure of 14 was confirmed by high resolution ^{1}H NMR,[13] IR, MS and elemental analysis.

Consistent MS, IR and ^{1}H NMR data, as well as good microanalyses values, were also obtained for the new compounds 3, 4, 6-9 and 11.

Conclusion

The present work describes one of the shortest and most efficient routes to C-nor D-homosteroids of the natural trans-anti-trans configuraiton. The yield of each step is good, except for the α-acetonylation sequence of the decalone 6. Indeed, our own results tend to show that, contrary to various recent literature claims, a truly general and efficient method for the α-acetonylation of ketones remains as yet undiscovered.

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