factors is available from the authors at the Institut de Chimie des Substances Naturelles.

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C-12 STEREOCHEMISTRY OF TEUPOLIN I AND RELATED DITERPENOIDS FROM *TEUCRIUM* SPECIES

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Key Word Index—*Teucrium* sp.; Labiatae; neo-clerodane diterpenoids; C-12 configuration.

Abstract—By ^{1}H NOE techniques, the configurations at the C-12 chiral centre have been assigned for 13 neo-clerodane diterpenoids isolated from *Teucrium* species. Contrary to recent suggestions in the literature, the experimental results indicate the C-12(S) stereochemistry for teupolin I.

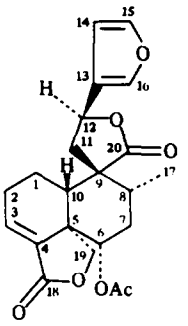
INTRODUCTION

Earlier, the absolute stereochemistry at the C-12 chiral centre of neo-clerodane diterpenoids isolated from *Teucrium* species was generally assumed to be *S*. This view was maintained by the fact that the few X-ray analyses and chemical correlations with compounds of known absolute stereochemistry were invariably made on *Teucrium* diterpenoids with the C-12(*S*) configuration. More recent studies employing ^{1}H NOE difference techniques [1, 2], however, have shown that the *S* configuration at C-12 is by no means a common stereochemical property in this class of natural products and, eventually, a revision of earlier assignments might be called for. In one of these works [1], the authors have found the C-12(*R*) configuration for a new neo-clerodane diterpenoid they had isolated from *T. scorodonia* [3] and *T. lanigerum* [4] and which, on the basis of some physical data (mp. $[\alpha]_D$, low frequency ^{1}H NMR), the authors claimed was identical to teupolin I (**13**), a diterpenoid from *T. polium*, isolated and described by us some years ago [5]. Since the physical data considered by the authors of ref. [1] are not necessarily distinctive for members of C-12 epimeric pairs, we have undertaken a detailed high-field ^{1}H NOE study on teupolin I and related diterpenoids from *Teucrium* species (**1**–**12**) also isolated by us previously [6–14]. In this respect it may be pointed out that the teupolin I sample used in the present study was of the same batch as the ones reported in refs [5] and [10].

RESULTS AND DISCUSSION

Stereochemical considerations show that *Teucrium* diterpenoids with the C-12(*R*) configuration have their Me-17 group and H-12 proton in a nearly parallel (*syn*) steric disposition on the same side of the lactone ring. The resulting spatial proximity can be easily monitored in selective DNOE experiments by irradiating either of the two pertinent resonances and observing the net enhancement of the other signal [15]. Performing these experiments on compounds **1**–**13** we have detected significant, 5–8%, enhancements with molecules **9** and **10** only, which suggested that the remaining diterpenoids belonged to the C-12(*S*) series.

While in ref. [1] the lack of enhancements in the aforementioned experiments was considered as a conclusive evidence for the C-12(*S*) stereochemistry, we have found that the spatial proximity arising from the altered configuration at C-12 (as well as from the concomitant changes in the lactone ring stereochemistry) can be readily



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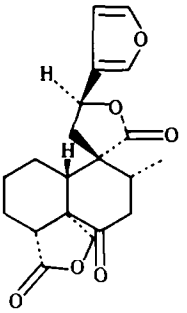

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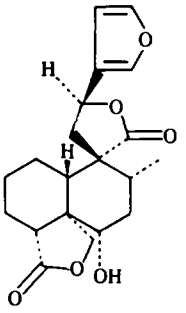

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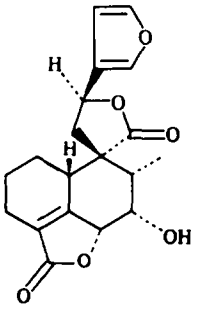

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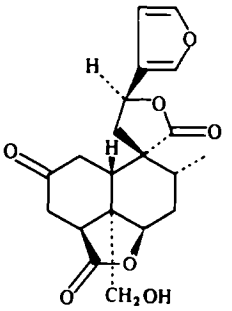

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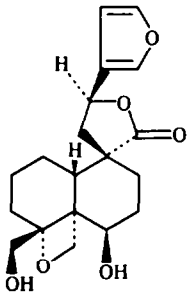

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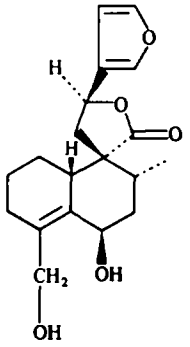

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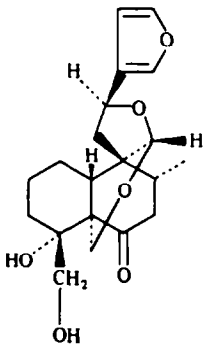

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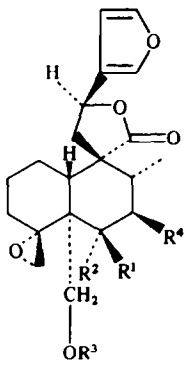
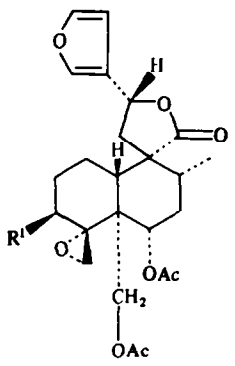
exploited at higher magnetic fields to gain direct, DNOE, evidence for the *S* stereochemistry. In fact, sizeable, 3–5 %, enhancements of the H-1β (equatorial) resonances were observed with molecules **1–8** and **11–13** upon selective low-power preirradiation of the proton signal due to H-12. These results clearly show that, contrary to statements in ref. [1], teupolin I (**13**) *does in fact* belong to the C-12 (*S*) series of neo-clerodanes.

We believe that doubts raised by the authors of ref. [1] with regard to the identity of teupolin I samples used by us in refs [5] and [10] were based mainly on the differences between the mp of teupolin I (211–213°, [5]) and those of teucjaponin B (255–258°, [16]) and the product obtained via reduction of 19-acetylgnaphalin (**14**) (256–259°, [17]), molecules that have an identical stereochemistry (**13**). Since differences in mp may arise from impurities and/or polymorphism, we have recrystallized our sample using the same solvent mixture as that used in ref. [1] and found a new mp of 254–257°, in complete agreement with the values found for teucjaponin B and reduced 19-acetylgnaphalin.

In order to avoid future confusions regarding the identity of teupolin I, we suggest the reinstatement of the original nomenclature: the name teupolin I should be retained for the C-12(*S*) molecule isolated from *T. polium*, whereas its C-12(*R*) enantiomer, extracted from *T. scorodonia* and *T. lanigerum*, should be termed as 12-epi-teupolin I.





11 $R^1 + R^2 = =O$, $R^3 = Ac$, $R^4 = OH$*
12 $R^1 = H$, $R^2 = OAc$, $R^3 = H$, $R^4 = H$
13 $R^1 = H$, $R^2 = OH$, $R^3 = Ac$, $R^4 = H$
14 $R^1 + R^2 = =O$, $R^3 = Ac$, $R^4 = H$

9 $R^1 = H$
10 $R^1 = OH$

* Modified structure for teupolin IV [11]

EXPERIMENTAL

Homonuclear selective $^1H-\{^1H\}$ NOE data were obtained by the difference (DNOE) method [15] at 400, 300 and 200 MHz for dilute $CDCl_3$ or $CDCl_3$–DMSO-d_6 solns of the samples using the frequency cycling technique [18] for selective preirradiation.

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