Pergamon

Tetrahedron Letters, Vol. 35, No. 23, pp. 3961-3964, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0714-9

Absolute Stereochemistry of Non-adjacent Bis-tetrahydrofuranic Acetogenins

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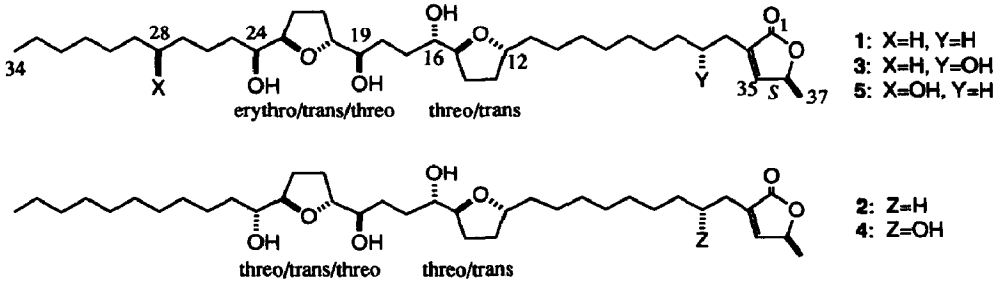
Abstract: Absolute stereochemistry of non-adjacent bis-tetrahydrofuranic acetogenins has been established by comparison of the ^{1}H-NMR data of their MTPA esters with those of optically active model tetrahydrofurans. 12*R*, 15*S*, 16*S*, 19*R*, 20*R*, 23*R*, 24*S* configuration was assigned for squamostatins-B and -D, whereas 12*R*, 15*S*, 16*S*, 19*R*, 20*R*, 23*R*, 24*R* configuration was assigned for squamostatins-C and -E.

Annonaceous acetogenins have attracted much interest these years because of a wide range of biological activities and unique structures.[1] These tetrahydrofuranic acetogenins are classified into three types according to the numbers of tetrahydrofuran rings and their connection patterns, *i.e.*, mono-tetrahydrofuran, adjacent bis-tetrahydrofuran and non-adjacent bis-tetrahydrofuran.[1] The determination of all the stereochemical issues has been an important concern because of their multiple stereogenic centers. McLaughlin's group[2] and ours[3] have recently developed a method to predict absolute configuration of the adjacent bis-tetrahydrofuran moiety of the second type of acetogenins. However, little has been known on the absolute configuration of the third type of acetogenins. The determination of the absolute stereochemistry of the non-adjacent bis-tetrahydrofuran moiety of squamostatins-D (**1**), -E (**2**), -B (**3**), -C (**4**) and -A (**5**), which were recently isolated from the seeds of *Annona squamosa*,[4-6] is described in this paper.



The stereochemistry, C-15/C-16-*threo*, C-19/C-20-*threo*, C-23/C-24-*erythro*, was assigned for **1**, **3** and **5**, whereas C-23/C-24-*threo* was assigned for **2** and **4** by the application of Born's rule.[5,6] Further, *trans* orientation of two substituents on two tetrahydrofuran rings (C-12/C-15-*trans* and C-20/C-23-*trans*) was also established for **1**-**5** by ^{13}C-NMR comparison with stereochemically defined model mono-tetrahydrofurans.[6] Moreover, the absolute configuration of the lactone moiety was determined to be 36*S* for **1**-**5**, and 4*R* for **3** and **4**.[2,6]

Table I. Differences in the Chemical Shifts (Δ_{S-R} Values in δ) between (*R*)- and (*S*)-MTPA Esters of **1** and **2**[a]

	H_2-11	H-12	H_2-13	H_2-14	H-15	H-16	H_2-17	H_2-18	H-19	H-20	H_2-21	H_2-22	H-23	H-24	H_2-25
1	+0.30 +0.30	+0.14	+0.18 +0.14	+0.15 +0.10	+0.10	+0.10	-0.06 -0.06	+0.11 +0.11	-0.04	+0.12	-0.09 -0.04	-0.06 -0.03	-0.09	-0.08	-0.07 -0.07
2	+0.05 +0.05	+0.12	+0.14 +0.14	+0.14 +0.14	+0.07	+0.08	-0.08 -0.08	+0.05 +0.05	-0.16	-0.20	-0.40 -0.31	-0.27 -0.20	-0.10	-0.09	+0.01 +0.01

[a] The methylene protons were assigned on the basis of the H-H COSY spectra.

We initially applied an advanced Mosher method[7] for prediction of the absolute configuration of the stereogenic centers in non-adjacent bis-tetrahydrofuran moiety. Table I summarizes the Δ_{S-R} values, which were obtained from the ^{1}H-NMR data of tri-(*R*)- and (*S*)-MTPA esters of **1** and **2**. It can be predicted that both **1** and **2** have 16*S* configuration (therefore, 12*R*, 15*S*, 16*S*) in terms of the positive Δ_{S-R} values for H-11 to H-15. Further, the relatively large negative Δ_{S-R} values of H_2-21 and H_2-22 may suggest that **2** has 19*R*, 24*R* configuration. However, it seemed to be difficult to predict the absolute stereochemistry of all stereogenic centers of **1**. The ^{1}H-NMR comparison studies were carried out for (*R*)-MTPA esters of stereochemically defined model compounds to overcome this difficulty and to confirm the assignment described above. It can be anticipated that the chemical shift of H-12 of tri-(*R*)-MTPA ester of **1** would be significantly influenced by the C-16-OMTPA group, but much less by C-19- and C-24-OMTPA groups. Similarly the chemical shift of H-24 would be influenced significantly by C-19-OMTPA group, but not much by C-16-OMTPA group. In this line, the chemical shift of H-12 of tri-(*R*)-MTPA ester (**1a**) of **1** was compared with those of (*R*)-MTPA esters of *threo*, *trans*-(2*R*,5*S*)-2-heptyl-5-(1-hydroxyheptyl)tetrahydrofuran (**6**) and its antipode (**7**).[8] The chemical shift of H-12 of **1a** was in good agreement with that of **6**, rather than **7**, thus strongly supporting that **1** has 12*R*, 15*S*, 16*S* configuration (Fig. 1). Similarly the comparison of the chemical shift of H-24 of **1a** with those of di-(*R*)-MTPA esters of *erythro*, *threo*, *trans*- (2*R*,5*R*)-di-(1-hydroxypentyl)-tetrahydrofuran (**8**) and its antipode (**9**) concluded that **1** has 24*S* configuration. These results imply that **1** has 12*R*, 15*S*, 16*S*, 19*R*, 20*R*, 23*R*, 24*S* absolute configuration. Similar ^{1}H-NMR comparison (Fig. 2) of tri-(*R*)-MTPA ester (**2a**) of **2** with those of **6** and **7** as well as *threo*,*threo*,*trans*-(2*R*,5*R*)-di-(1-hydroxypentyl)-tetrahydrofuran (**10**) and its antipode (**11**)[8] established that **2** has 12*R*, 15*S*, 16*S*, 19*R*, 20*R*, 23*R*, 24*R*.

The same stereochemistry as in **1** was assigned for **3** because the chemical shifts of the oxymethine protons of non-adjacent bis-tetrahydrofuran moiety of tetra-(*R*)-MTPA ester of squamostatin-B (**3**) were essentially identical with those of **1a**. Similarly the absolute configuration of **4** was determined to be the same as **2**.

Squamostatin-A (**5**) is a C-28 hydroxylated non-adjacent bis-tetrahydrofuranic acetogenin.[4] The absolute stereochemistry of **5** could be predicted as follows. The chemical shifts of H-12, -15, -16, -19, and -20 of tetra-(*R*)-MTPA ester (**5a**) of **5** were essentially identical to those of **1** and **3**. The chemical shifts of H-23 and H-24 of **5a** were shifted upfield by *ca.* δ 0.08 and 0.10, respectively, from the corresponding signals of **1a**. The same magnitude of upfield shifts was observed in the chemical shifts of H-23 and H-24 of (*R*)-MTPA esters of squamocin[9] and its 28-deoxy compound (squamocin-L).[3] Therefore, it can be assumed that **5** has 12*R*, 15*R*, 16*S*, 19*R*, 20*R*, 23*R*, 24*S*, 28*S* configuration.

In conclusion, we have established the configuration of all the stereogenic centers in the non-adjacent bis-tetrahydrofuran moiety by comparing the chemical shifts of H-12 and H-24 separately with those of the appropriate model MTPA esters. This is the first report on the absolute configuration of two stereochemical types (**1**,**3** and **5** *vs.* **2** and **4**) of non-adjacent bis-tetrahydrofurans. To date approximately ten acetogenins

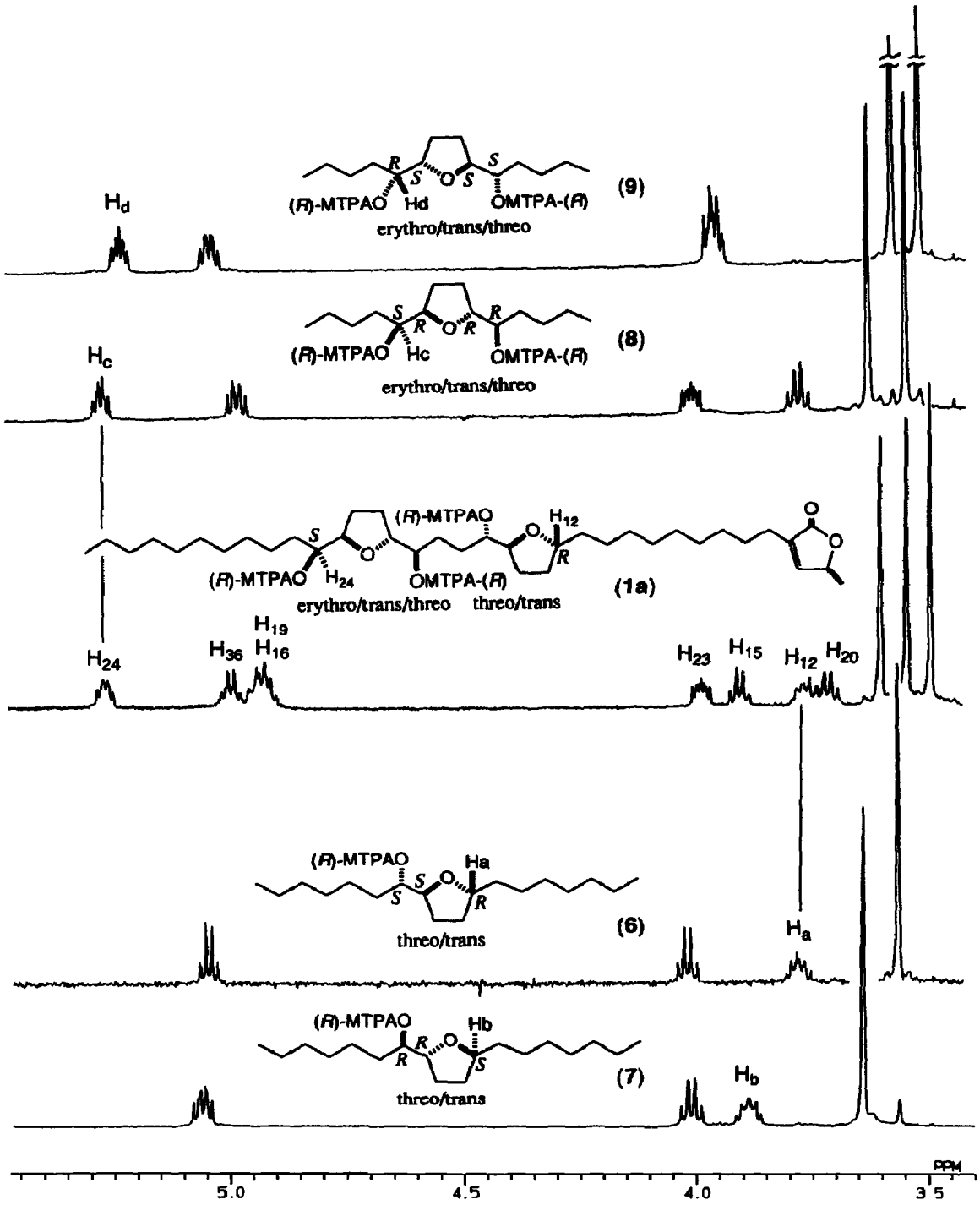


Fig. 1. ^{1}H-NMR Comparison of **1a** and **6-9** (500 MHz, $CDCl_3$)

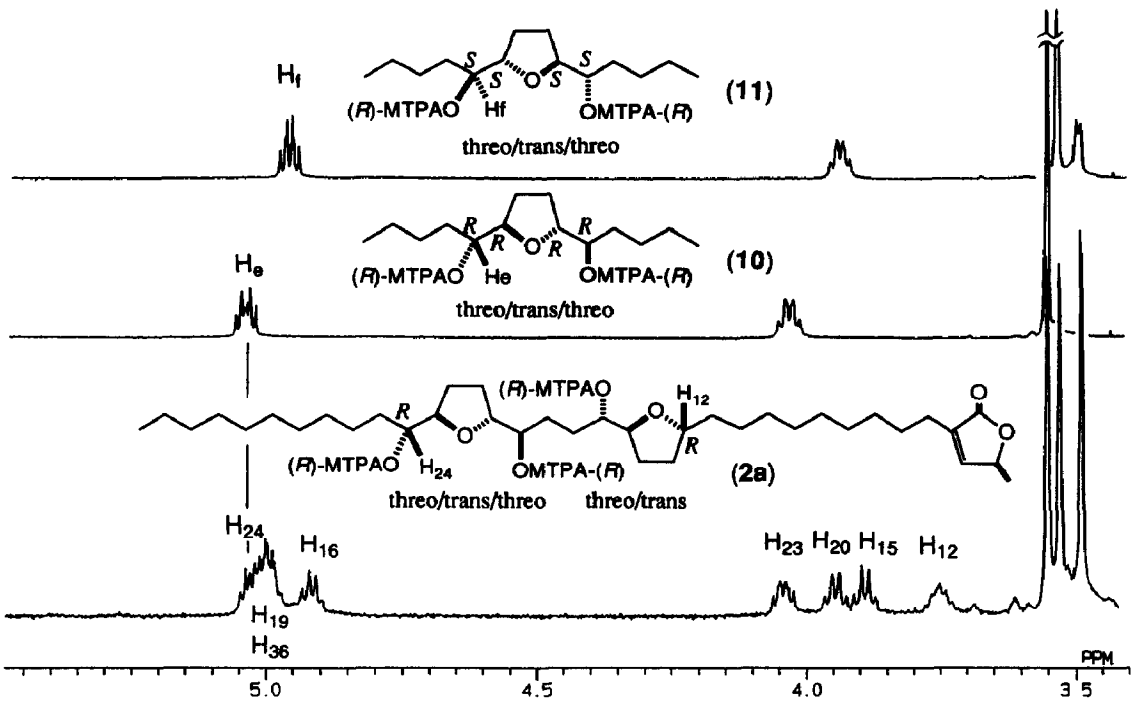


Fig. 2. ^{1}H-NMR Comparison of **2a**, **10** and **11** (500 MHz, $CDCl_3$)
(For comparison with **6** and **7**, refer Fig. 1)

of this type have been reported. We strongly recommend that this type of acetogenins should be defined stereochemically on the basis of the ^{1}H-NMR data of (*R*)-MTPA esters presented in this paper.

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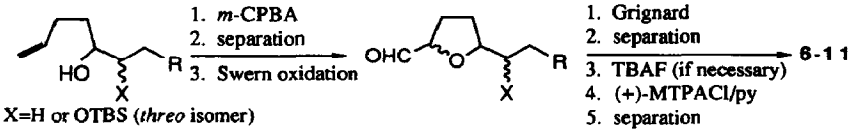
8) The model compounds were synthesized in a non-stereoselective manner as follows. The *trans* and *cis* stereochemistry was determined by NOE experiments and the absolute stereochemistry of **6**-**11** was deduced by advanced Mosher method.[7]



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(*Received in Japan* 1 *November* 1993; *accepted* 14 *January* 1994)