AQUEOUS DIELS-ALDER REACTIONS OF ELECTRON DEFICIENT 2-ARYLFURANS: A HIGHLY STEREOSELECTIVE ROUTE TO 2,2,5-TRISUBSTITUTED TETRAHYDROFURANS TOWARDS A NOVEL CLASS OF ORALLY ACTIVE AZOLE ANTIFUNGALS**

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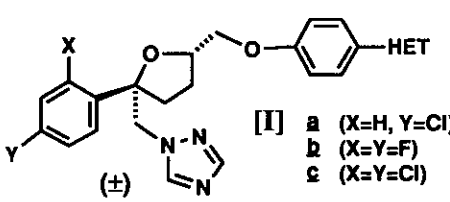
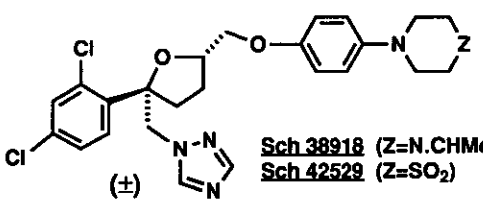
Abstract- Aqueous Diels-Alder reactions[1] of halogenated 2-arylfurans with acetylenedicarboxylates made available previously inaccessible adducts (**2**, **2a**, **7**, and **8**) which were successfully elaborated in a general stereocontrolled route to the title compounds.

Treatment of systemic fungal infections is a serious problem particularly with regard to opportunistic infections commonly found in cancer, AIDS and organ transplant patients.[2] As part of an extensive search for orally effective agents, we recently reported on a series of novel 2,2,5-trisubstituted tetrahydrofurans of the type [**I**] with broad-spectrum antifungal activity.[3] The active compounds have a cis relationship between the triazolylmethyl group and a 4-substituted lipophilic phenyl ether moiety; the trans analogs lacked in vitro as well as in vivo activity. **Sch 38918** and **Sch 42529** are two of several analogs having in vivo activity superior to ketoconazole,[2] a well known orally effective antifungal agent.



[**I**] **a** (X=H, Y=Cl)
b (X=Y=F)
c (X=Y=Cl)



Sch 38918 (Z=N.CHMe$_2$)
Sch 42529 (Z=SO$_2$)

One drawback of our early route[3] to type [**I**] compounds was the lack of stereocontrol resulting in the cis and the undesired trans isomers in comparable amounts. In seeking a stereoselective route to the cis compounds a Diels-Alder reaction between 2-arylfurans (**1**, **5**, and **6**) and a suitable dienophile appeared most appropriate. The only Diels-Alder reaction between a halogenated 2-arylfuran (**1**) and diethyl acetylenedicarboxylate under conventional (thermal) conditions was reported to provide **4**, the product of retrogade Diels-Alder process, as the only isolable product.[4,5] In the present work attempted isolation of the primary adduct (**2**) under the same conditions proved unavailing due to complexity of the reaction mixture. However, partial hydrogenation of the crude reaction mixture followed by repeated chromatography provided the dihydro product (**3**) albeit in 5- 10% yields.[6]

** Dedicated to Professor Edward C. Taylor on occasion of his 70th birthday

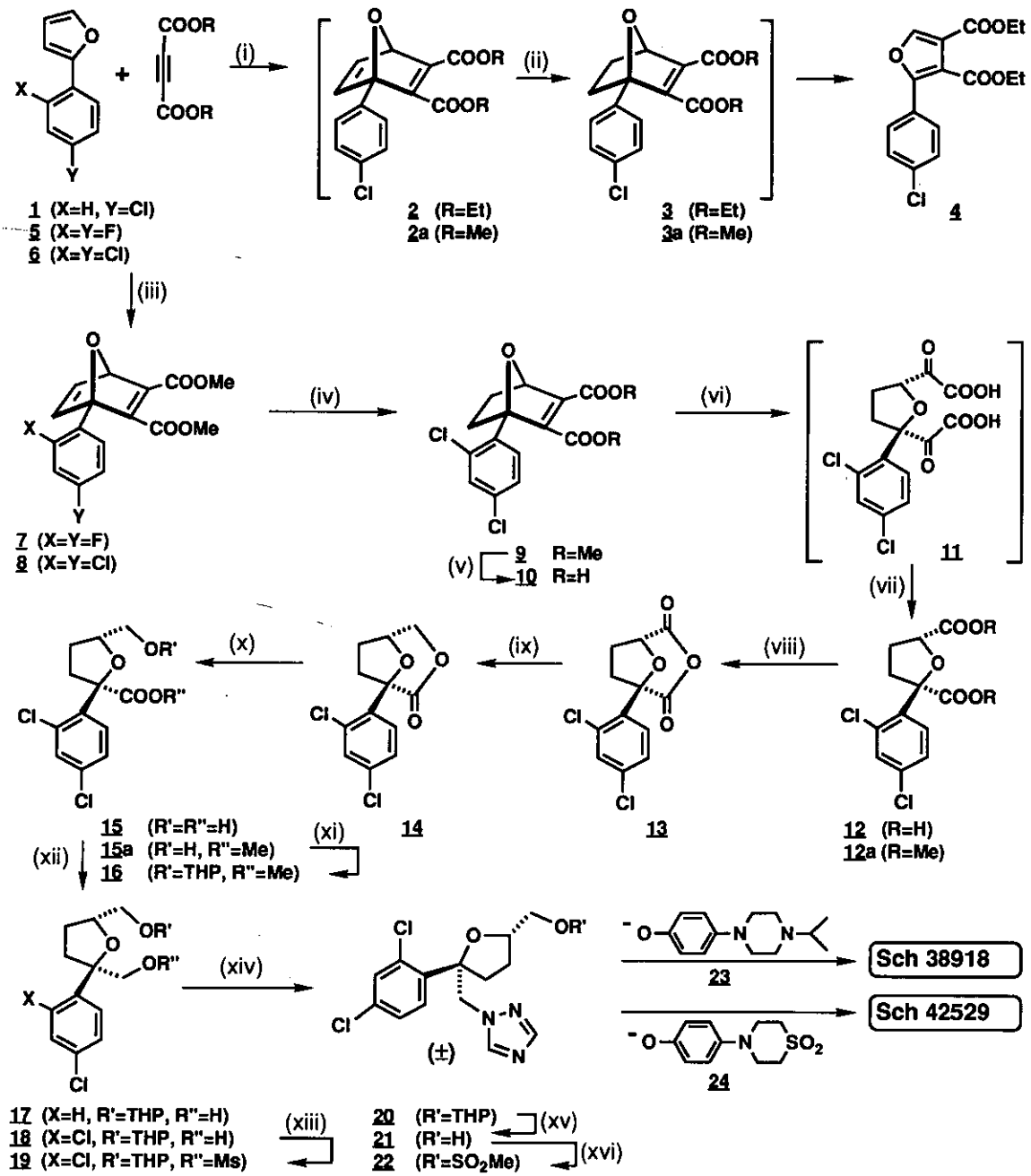
Breslow and Rideout reported dramatic rate acceleration of certain Diels-Alder reactions in aqueous suspensions, a result ascribed largely to hydrophobic association of the diene with the dienophile.[1] Thus, it appeared likely that Diels-Alder reactions of 2-arylfurans (**1**, **5**, and **6**)[6-9] in water might proceed at a much lower temperature, avoiding the undesired retro reaction. Indeed, when **1** and dimethyl acetylenedicarboxylate were mixed in water and the heterogenous system sonicated in a stoppered flask (~24 h), the reaction mixture consisted of virtually a single product.[10] Simple chromatography provided **2a** as a crystalline solid mp 84°C in over 90% yield.[11] Selective catalytic hydrogenation of the disubstituted double bond yielded **3a**, mp 90-91°C (95% yield).[12] Similarly aqueous Diels-Alder reactions of the 2-(2,4-dihalophenyl)furans (**5**) (oil) and (**6**) (mp 34°C) provided the primary adducts (**7**), mp 53-55°C, and (**8**), mp 83-84°C in over 60% and 90% yields respectively.[13,14] This remarkable improvement allowed syntheses of a large variety of broad-spectrum orally active antifungals of the type [**I**],[3] exemplified by stereoselective syntheses of **Sch 38918** and **Sch 42529** (Scheme 1).

Controlled catalytic hydrogenation of **8** (H_2/Pt) at room temperature and atmospheric pressure gave the dihydro compound (**9**) in excellent yield.[15] Decarboxylative oxidative cleavage of **9** was accomplished in the following manner. Hydrolysis with aqueous NaOH in THF provided the diacid (**10**), mp 145-147°C in ~95% yield.[15] Ozonolysis of **10** in MeOH:CH_2Cl_2 followed by Me_2S work-up[16] gave the crude dipyruvic acid (**11**) which was used as such. Treatment of **11** with aqueous NaOH followed by 30% H_2O_2 (ice bath cooling) readily afforded the diacid (**12**) (~90% yield).[17] The most convenient reagent to effect the conversion of the diacid (**12**) to the anhydride (**13**) was ethoxyacetylene,[18,19] and treatment of **12** with this reagent in CH_2Cl_2 directly provided the anhydride (**13**),[20] which was sufficiently pure for the next reaction. Sodium borohydride reduction of **13** in THF/MeOH,[21] took place regioselectively at the less hindered carbonyl to provide the δ-lactone (**14**),[22] mp 136-137°C (81% yield) which could be hydrolysed with mild base to the hydroxy acid (**15**), mp 150-151°C. Methylation of **15** with CH_2N_2 then gave the hydroxy ester (**15a**).[23] Alternatively, treatment of the δ-lactone (**14**) with CH_2N_2 in methanol directly gave the hydroxy ester[24] (**15a**) in ~100% yield. Protection of **15a** with dihydropyran under standard conditions gave the THP ether (**16**) as a key intermediate.

When **16** was treated with $LiAlH_4$ in ether under reflux, concomitant reduction of the ortho-chloro substituent was observed besides the expected reduction of the ester functionality affording **17** in ~70% yield.[25] In marked contrast, treatment of **16** with $LiAlH_4$ in the same solvent at room temperature (~22°C) provided the expected alcohol (**18**) (85% yield) uncontaminated by **17**. Thus, **16** served as a convenient intermediate for analogs of the type [**I**]a as well as [**I**]c. The final steps were easily accomplished in the following manner.

Reaction of **18** with mesyl chloride in pyridine gave the mesylate (**19**) in ~100% yield. Treatment of **19** with sodium salt of 1,2,4-triazole in DMF containing 10% DMPU at 100°C for ~24 h afforded the 1-N-triazolyl substituted product (**20**) (80% yield), and acid catalysed deprotection of the THP group (to provide **21**)[26] followed by mesylation furnished **22** in ~90% yield from **20**. The mesylate (**22**) acted as a central intermediate to provide a host of novel analogs of the type [**I**]c.[3] For example, coupling of **22** with phenoxide anions (**23**)[27] and (**24**)[28] in DMSO (80°C, ~4 h) afforded **Sch 38918**,[29] mp 107-109°C and **Sch 42529**,[30] mp 162-163°C in 70% and 65% yields respectively.

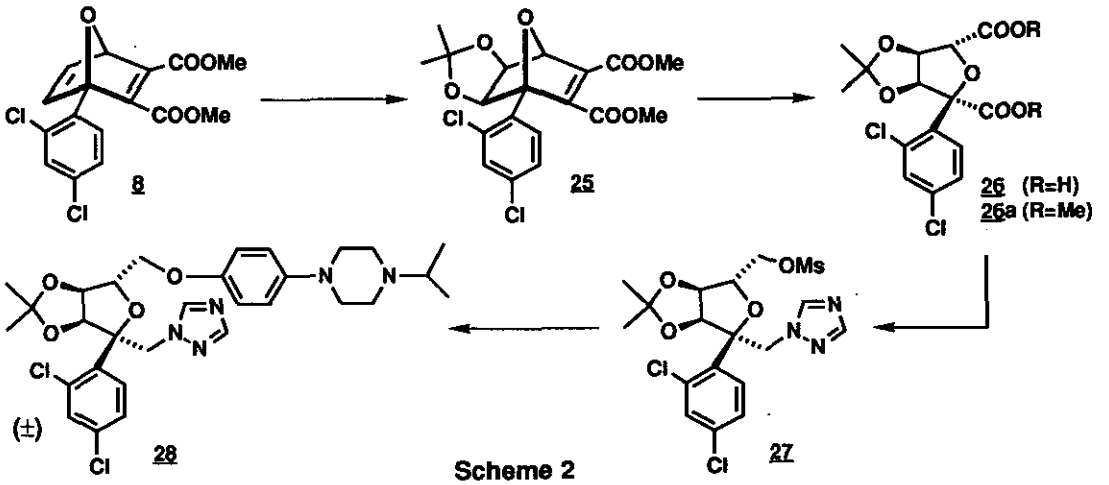
It may be noted that highly functionalized 1-aryl-7-oxabicyclo[2.2.1]hept-2,5-diene-2,3-dicarboxylates of the types (**2**, **7**, and **8**) offer a variety of possibilities for stereoselective transformations. Thus, in an extension of the above methodology, catalytic osmylation[31] of **8** followed by treatment with acetone in the presence of P_2O_5



Reaction Conditions and Reagents: (i) 120° C; (ii)Pt/ H_2; (iii) H_2O/Sonication / 22-45° C; (iv) Pt/H_2; (v) Aq. NaOH/MeOH; (vi) O_3/MeOH-CH_2Cl_2, Me_2S work-up; (vii) H_2O_2/Aq. NaOH; (viii) ≡—OEt /CH_2Cl_2; (ix) $NaBH_4$/MeOH; (x) CH_2N_2/MeOH; (xi) Dihydropyran/PPTS; (xii) **16** to **17** : LAH/EtOEt, reflux; **16** to **18** : LAH/EtOEt, room temperature; (xiii) MsCl/Pyridine; (xiv) Na-triazole/DMF/100° C; (xv) 6N HCl/Dioxane; (xvi) MsCl/Pyridine.

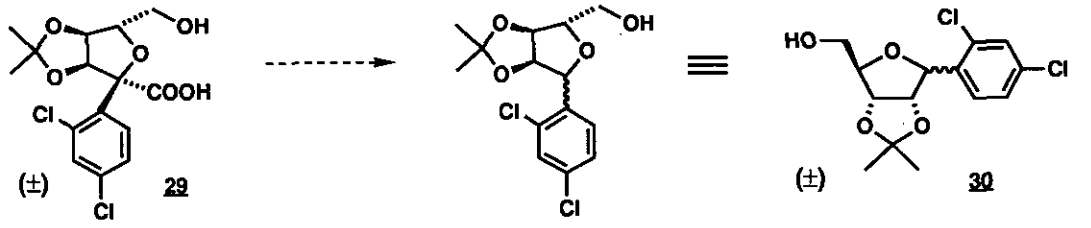
Scheme 1

provided **25** (>90% yield).[32] Following the synthetic transformations **9** → **18**, **25** was efficiently converted to the diacid (**26**) which served as a useful intermediate for modified analogs such as **28** mp 152-153°C (via **27**), as depicted below (Scheme 2).[33]



Scheme 2

A further use of the Diels-Alder adducts of the type described here may be in a convenient approach to electron deficient C-1 aryl derivatives of ribose. Direct C-1 arylations of ribose using electron rich aromatic groups under Lewis acid catalysis have been reported,[34] but such direct C-1 arylations are not possible with electron deficient aromatic systems. However, hydroxy acid intermediates such as **29** may be decarboxylated, for example by recent radical chemistry[35] to provide novel C-1 aryl ribose derivatives such as **30** (Scheme 3).



Scheme 3

Diels-Alder reaction of **6** with dimethylacetylene dicarboxylate in the $LiClO_4$-Et_2O system[36] also proceeded smoothly to provide **8** in over 90% yield. In the present context however, we find the aqueous version of the Diels-Alder reaction[1] operationally safer and extremely convenient to scale-up.

We intend to extend the scope of aqueous Diels-Alder reactions of 2-aryl furans to other dienophiles.[37] We shall also report on the utility of the above intermediates including the hydroxy acid (**29**) in future publications.

ACKNOWLEDGEMENTS

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5 Attributed to the dominant retro reaction, a subsequent attempt also failed to provide the primary Diels-Alder adduct **2**; see: D.C. Ayres and J.R. Smith, *J. Chem. Soc.*, (C), **1968**, 2737.
6. All new compounds were characterized by high resolution mass spectra, ^1H and ^{13}C nmr spectra. When necessary ^1H-^1H decoupling experiments were performed. Elemental analyses were obtained for crystalline compounds only. Yields refer to isolated products. Selective spectral data is given.
7. The 2-arylfurans (**1** and **6**) were prepared according to ref.4 and **5** according to ref. 9.
8. **5:** ^1H Nmr [$CDCl_3$] δ 6.54 (q, finely split, 1H), 6.82 (q, finely split, 1H), 6.87-6.99 (m, 2H), 7.50 (d, finely split, 1H), 7.83 (m, 1H).

   6: ^1H Nmr [$CDCl_3$] δ 6.53 (q, finely split, 1H), 7.12 (q, finely split, 1H), 7.27 (d, J=2.0 Hz, 1H), 7.32 (d, J=2.2 Hz, 1H), 7.45 (d, J=2.4 Hz), 7.51 (q, finely split, 1H), 7.78 (d, J=8.2 Hz, 1H).
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10. **Typical procedure: 6** (18 g, 85 mmol) + dimethyl acetylenedicarboxylate (14.7 ml, 120 mmol) in water (60 ml) were sonicated in a stoppered flask (protected from light) for ~24 h. The temperature ranged from ~22°C to ~45°C during the course of reaction. Extractive isolation with CH_2Cl_2 provided a orange gum. It was chromatographed on a short SiO_2 column using 10% acetone/n-hexane to provide pure **8** as a crystalline solid (19.5 g, 65%). Some early fractions provided pure unreacted 2-arylfuran **6** (6 g, 33%). Reactions carried out strictly at room temperature proceeded cleanly but at a much slower rate.
11. **2a:** ^1H Nmr [$CDCl_3$] δ 3.68 (s, 3H), 3.80 (s, 3H), 5.85 (d, J=1.2 Hz, 1H), 7.30-7.50 (m, 6H).
12. **3a:** ^1H Nmr [$CDCl_3$] δ 3.60 (s, 3H), 3.80 (s, 3H), 5.37 (d, J=4.8 Hz, 1H), 7.34 (d, J=8.8 Hz, 2H), 7.40 (d, J=8.8Hz, 2H).
13. **7:** ^1H Nmr [$CDCl_3$] δ 3.68 (s, 3H), 3.80 (s, 3H), 5.77 (d, J=1.95 Hz, 1H), 6.87-6.93 (m, 2H), 7.32-7.34 (q, finely split, 1H), 7.43-7.50 (m, finely split, 2H).
14. **8:** ^1H Nmr [$CDCl_3$] δ 3.70 (s, 3H), 3.84 (s, 3H), 5.76 (d, J=1.2 Hz, 1H), 7.30-7.58 (m, 5H).
15. Hydrogenation was promptly terminated after ~1.1 molar equivalent hydrogen uptake. In one instance, when the desired **9** was inadvertantly left in contact with hydrogen in the presence of Pt catalyst overnight, the only product obtained was the fully saturated diester, mp 100-102°C.

    9: ^1H Nmr [$CDCl_3$] δ 1.65-1.78 (m, 1H), 2.10-2.29 (m, 2H), 2.30-2.45 (m, 1H), 3.67 (s, 3H), 3.80 (s, 3H), 5.37 (d, J=4.4 Hz, 1H), 7.27 (q, finely split, 1H), 7.40 (d, J=2.2 Hz, 1H), 7.57 (d, J=9.0 Hz, 1H).

    10: ^1H Nmr [$CDCl_3$] δ 1.55-1.70 (m, 1H), 1.85-1.98 (m, 1H), 2.20-2.35 (m, 1H), 2.42-2.55 (m, 1H), 5.51 (d, J=5.2 Hz, 1H), 7.31 (q, 1H), 7.42 (d, J=1.6 Hz, 1H), 7.56 (d, J=8.4 Hz, 1H).
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17. **Procedure:** A solution of the diacid (**10**) (8 g, 24.4 mmol) in MeOH:CH_2Cl_2, (1:1, 75 ml) was ozonized (acetone/dry ice bath) until blue color persisted. Excess ozone was flushed by argon, Me_2S (2.4 ml) was added and the reaction was allowed to warm up to -10°C (bath temperature). After 1 h the temperature was raised to 0°C and kept for another hour. The solvents were evaporated in-vacuo (temp.~40°C) and to the gummy residue was added with cooling (ice bath) 40% NaOH (8 ml, 80 mmol) followed by 30% H_2O_2 (8 ml, 70 mmol). Copious elimination of CO_2 took place after a brief (~5 min.) induction period. The reaction mixture was left in the freezer compartment overnight, diluted with water (~40 ml) and the almost pure diacid (**12**) (7.2 g, 96%) was isolated by extractive work-up with ethyl acetate. It was purified as the diester (**12a**) and regenerated by hydrolysis to **12**, mp 152-153°C.

    12: ^1H Nmr [$CDCl_3$] δ 2.30-2.60 (m, 3H), 2.90 (m, 1H), 4.73 (t, finely split, 1H), 7.30 (dd, J=2.4, 8.2 Hz, 1H), 7.34 (d, J=2.4 Hz, 1H), 7.67 (d, J=8.2 Hz, 1H).
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20. **13:** ^1H Nmr [$CDCl_3$] δ 1.20-1.30 (m, 1H), 2.20-2.60 (m, 2H), 2.85-3.05 (m, 1H), 5.18 (dd, J=2.4, 7.8 Hz, 1H), 7.30 (dd, J=2.2, 8.4 Hz, 1H), 7.50 (d, J=2.2 Hz, 1H), 7.56 (d, J=8.4 Hz, 1H).
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carbon, this does not seem to be as general for 6-membered cyclic anhydrides. See for example: B.E. Cross and J.C. Stewart, *J. Chem. Soc.*, (C), **1971**, 246; and cited references.

22. **Procedure:** A stirred and cooled (ice bath) solution of the anhydride **13** (ex. 1 g, 3.2 mmol diacid **12**) in dry THF (6 ml) was treated with $NaBH_4$ (0.13 g, 3.4 mmol). The reaction was stirred for 1 h followed by dropwise addition of methanol (~2 ml) until gas evolution subsided. After 3 h stirring, the reaction mixture was acidified to pH 1 with 6N HCl and extracted with CH_2Cl_2 (4×40 ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness in vacuo. The residue was dissolved in 5 ml acetone and kept in fridge (3 days) when the lactone (**14**), (0.7 g, 81%) crystallized out (mp 136-137°C).

    14: ^{1}H Nmr [$CDCl_3$] δ 1.90-2.00 (m, 1H), 2.10-2.20 (m, 1H), 2.20-2.38 (m, 1H), 3.05-3.10 (m, 1H), 3.12 (dd, J=3.4, 11.7 Hz, 1H), 3.96 (dd, J=3.0,11.7, 1H), 4.36 (m, 1H), 7.28 (q, finely split, 1H), 7.4 (dd, finely split, 1H), 7.58 (d, J=8.6 Hz, 1H).
23. **15a:** ^{1}H Nmr [$CDCl_3$] δ 1.90-2.00 (m, 1H), 2.05-2.20 (m, 2H), 2.25-2.40 (m, 1H), 3.10-3.20 (m,1H), 3.62 (dd, J=4, 12 Hz, 1H), 3.7 (s, 3H), 3.82 (dd, J=3.0, 12 Hz, 1H), 4.38 (m, 1H), 7.27 (dd, J=2.1, 8.5 Hz, 1H), 7.36 (d, J=2.1 Hz), 7.62 (d, J=8.5 Hz, 1H).
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26. **21:** ^{1}H Nmr [$CDCl_3$] δ 1.85-2.00 (m, 2H), 2.25-2.35 (m, 1H), 2.70-2.80 (m, 1H), 3.53 (dd, J=3.18, 12.24 Hz, 1H), 3.84 (m, 1H), 3.96 (dd, J=3.18, 12.24 Hz, 1H), 7.19 (dd, J=1.7, 8.6 Hz, 1H), 7.43 (s, 1H), 7.44 (d, J=8.6 Hz, 1H), 7.76 (s, 1H), 7.89 (s, 1H).
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30. **Sch 42529:** ^{1}H Nmr [$CDCl_3$] δ 1.39 (m, 1H), 1.86 (m, 1H), 2.40 (m, 1H), 2.72 (m, 1H), 3.20 (m, 4H), 3.72 (m, 4H), 3.90 (dd, finely split, 1H), 4.00 (dd, finely split, 1H), 4.29 (m, 1H), 4.52 (d, finely split, 1H), 4.85 (d, finely split, 1H), 6.91 (d, finely split, 2H), 6.96 (d, finely split, 2H), 7.24 (s, 1H), 7.44 (1H), 7.62 (s, 1H), 7.89 (s, 1H), 8.23 (s, 1H).
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32. **25:** ^{1}H Nmr [$CDCl_3$] δ 1.34 (s, 3H), 1.36 (s, 3H), 3.69 (s, 3H), 3.79 (s, 3H), 4.75 (d, J=5.4 Hz, 1H), 5.13 (s, 1H), 5.33 (d, J=5.4 Hz, 1H), 7.28 (dd, J=2.0, 8.6 Hz, 1H), 7.39 (d, J=2.0 Hz, 1H), 7.70 (d, J=8.6 Hz, 1H).

    26a: ^{1}H Nmr [$CDCl_3$] δ 1.24 (s, 3H), 1.29 (s, 3H), 3.69 (s, 3H), 3.76 (s, 3H), 4.81 (s, 1H), 5.38 (dd, J=1.4, 5.8 Hz, 1H), 5.60 (dd, J=5.8 Hz, 1H), 7.29 (dd, J=2.2, 8.4 Hz, 1H), 7.36 (d, J=2.2 Hz, 1H), 7.75 (d, J=8.4 Hz,1H)
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