Revisiting Curcumin Chemistry Part I: A New Strategy for the Synthesis of Curcuminoids

E. VENKATA RAO* AND P. SUDHEER
Natco Research Centre, B-13, Industrial Estate, Sanathnagar, Hyderabad - 500 018, Andhra Pradesh, India

Rao and Sudheer: New Strategy for Synthesis of Curcuminoids

A new strategy for the synthesis of curcuminoids is described involving the reaction of acetylacetone difluroboronite with an aromatic aldehyde in the presence of n-butylamine as catalyst. The new intermediate products, curcuminoid difluroboronites, of symmetrically substituted curcuminoids like curcumin and bisdemethoxycurcumin are stable, can be isolated and hydrolysed with aq. methanol at pH 5.8 to get the curcuminoids of high purity. The method is applicable for unsymmetrical curcuminoids like demethoxycurcumin also with some modification involving column chromatography. The intermediate curcuminoid difluroboronites, as also the natural β-diketone pongamol difluroboronite, prepared for the first time were characterized on the basis of physical and chemical properties and spectroscopic data. The advantage of using borontrifluoride to protect the enol group in acetylacetone over the generally used boric oxide is brought out. The importance of conducting biological activity studies using pure curcuminoids is explained.

Key words: Curcuminoids, pongamol, difluroboronites, synthesis, structure, cleavage, β-Diketones

Turmeric (*Curcuma longa* Linn., Zingiberaceae) is extensively cultivated in India and other south-east Asian countries. In contrast to turmeric's limited use in western countries as a coloring agent, it is widely used in the countries of origin as a food additive and medicinal agent. The main components of turmeric are curcuminoids, which in general are 1,7-diaryl-1,6-diene-3,5-dione-heptanoids. Of these, curcumin (CI), demethoxycurcumin (CII) and bisdemethoxycurcumin (CIII) are important.

Curcumin has been reported to have a wide spectrum of biological activities, chiefly antibacterial, antioxidant, antitumor, and carcinogenic[1] and neurological[2]. Clinically curcumin has potential usefulness in treating post-operative inflammation[3], inflammatory bowel disease[4], debilitating illnesses like Crohn's disease or ulcerative colitis[5] and Alzheimier's disease[6].

Many of the biological activity studies were carried out on curcumin obtained from commercial sources, which could be mixtures of CI (1), CII (2) and CIII (3). The three components differ in their solubility and methoxy groups, which can influence the biological activity. In contrast to the general belief that CI is the most important active component of turmeric, there are a few biological activity studies carried out on pure components, obtained by isolation[7,8] or synthesis[9], which show that CIII is more potent than CI.

The isolation of pure compounds from turmeric is considered as a difficult and costly procedure. So far the three related compounds were separated by preparative TLC only. In connection with our work (unpublished) on the isolation of pure curcuminoids from turmeric, we turned our attention to synthetic aspects of curcuminoids to obtain pure samples for comparison[10].

The major processes of practical utility for the preparation of the symmetrical curcuminoids, CI and CIII, follow Pabon's route[11] involving the reaction of vanillin or 4-hydroxybenzaldehyde and acetylacetone in the presence of boric oxide, trialkylborate and a primary amine. The method was extended by Roughley and Whiting[12] using both vanillin and 4-hydroxybenzaldehyde for the synthesis of the unsymmetrical curcuminoid, CII. The synthetic strategy of Pabon was followed by Graf[13] omitting

*Address for correspondence
E-mail: erraguntlavrao@yahoo.co.uk

the use of trialkylborate, but heating at 120-130⁰. A US patent[14] described a process for the synthesis of CI and related compounds making use of boric oxide, trialkylborate along with a chemically inert, highly polar aprotic solvents, especially organic amides. The boron complex of acetylacetone and subsequent condensation with aldehyde produce water in the reaction system reducing the yield of CI and hence the need for trialkylborate as a water scavenger. Preparation of CI on laboratory scale as well as commercial scale invariably follow Pabon's route[11] with some variation.

As boric oxide is expensive Dinesh Babu and Rajasekharan[15] replaced it with boric acid. Their procedure involves purification by extensive column chromatography. Following Pabon's method[11], we tried to replace boric oxide with boric acid, but it did not work in our hands. Krackov and Bellis[14] reported an yield of 5% for CI when they replaced boric oxide with boric acid in their work. The purpose of boric oxide is to protect the enol group in acetylacetone to prevent the highly acidic methylene protons from Knoevenegal condensation such that the condensation can occur at the terminal methyl groups of the diketone.

Against this background we have tried an alternative procedure for protecting the enol group in acetylacetone for the synthesis of CI. Our patented process[10], involving the use of borontrifluoride in place of boric oxide, is elaborated and discussed in this paper covering the chemical and spectral aspects. Further the study was extended to the synthesis of CII and CIII.

While studying the chemical properties of CI (1), we had occasion to try borontrifluoride etherate (BF$_3$.Et$_2$O) in CHCl$_3$ medium at 0-5⁰ to effect demethylation[16]. No demethylation occurred but a hitherto unreported CI derivative was formed. When the reaction was carried out in Ac$_2$O-Et$_2$O medium, the corresponding diacetyl compound was formed with amazing ease. This was also the case with CII (2) and CIII (3). CI was chosen for a more detailed study.

A search in literature revealed that β-diketones (acetylacetone, benzoylacetone and dibenzoylmethane) react with BF$_3$.Et$_2$O in benzene solution affording chelated difluoroboronites[17], initially termed as boron-β-diketofluorides[18]. No spectral data is available in literature for comparative study. We have prepared for the first time such a derivative for pongamol[19,20], a natural β-diketone, besides the known acetylacetonedifluroboronite[18] (AADFB) (5) for our study. Since curcuminoids and acetylacetone are all β-diketones and react with BF$_3$.Et$_2$O in the same way, we envisaged that AADFB in which the enol group is already protected can be used in place of acetylacetone and boric oxide for curcuminoids synthesis.

MATERIALS AND METHODS

AADFB was prepared as per the procedure in literature[18]. TLC was carried out on silica gel 60 F$_{254}$ Merck precoated sheets in solvent system CHCl$_3$-MeOH (9.9:0.1) and (9.6:0.4) for curcuminoids and derivatives and Hexane-EtOAc (7:3) for pongamol and derivative. Column chromatography (CC) was carried out on silica gel 100-200 mesh. Aqueous methanol used for hydrolysis is methanol-water (80:20). Stirring during reaction was mechanical using magnetic stirrer or paddle stirrer depending on the volume of reaction mixture. HPLC was carried out on Novopak (150×3.9 mm) column using wavelength 248 nm for detection. Mobile phase was a mixture of acetonitrile and phosphate buffer (0.05M, pH 3) (500:500). RT stands for room temperature. Water used is demineralised water.

General procedure for the synthesis of CI and CIII (Scheme 1):

The aromatic aldehyde, vanillin or 4-hydroxybenzaldehyde (0.05 mol), was dissolved in EtOAc (40 ml) and AADFB (0.025 mol) added in small lots under stirring at RT. n-Butylamine (n-BuNH$_2$) (0.0045 mol) was added in small lots with a microsyringe over 40 min. After the addition, stirring was continued for 3-4 h. The solvent was distilled off from the reaction mixture.

Isolation of curcuminoid difluoroboronite:

To the reaction mixture, water (60 ml) was added followed by 1N HCl drop wise under heating at 60⁰ and stirring until a pH of 2-3 was reached. The separated red solid was filtered, washed free from acid with water and dried. A small portion was purified for spectral analysis by passing the acetone solution through a small column of silica gel and evaporating the acetone eluate. The above reaction

can be conducted in CHCl₃ medium in place of EtOAc, and morpholine can replace n-BuNH₂ as base catalyst. However, we occasionally observed unreacted aromatic aldehyde when morpholine was used.

Hydrolysis of curcuminoid difluoroboronites:

The difluoroboronite solid of CI (CIDFB) or CIII (CIIIDFB) was dissolved in aqueous MeOH (*ca.* 200 ml for 1 g of solid), the pH adjusted to *ca.* 5.8 by drop wise addition of 1% aqueous NaOH and heated at 70° under vigorous stirring for 3-4 h, when the deep red solution turned orange. Water was added and distilled under mild vacuum to remove most of the methanol. The resulting suspension was cooled to 15° under stirring and the solid formed (CI or CIII) was filtered, washed with water and dried. In cases where the product contained a small quantity of the unhydrolyzed product (colour and TLC), the product was dissolved in 5% aqueous NaOH and extracted with CHCl₃ to remove the impurity. The CHCl₃ layer was rejected. The alkali layer is immediately cooled to 5° and acidified to pH 3 with conc. HCl under stirring. The precipitated solid (CI or CIII) was filtered, washed free from acid with water and dried.

Following the above procedure CI and CIII were prepared using the quantities mentioned here (as

an example). CI from vanillin (9.5 g, 0.062 mol), AADFB (4.65 g, 0.031 mol), n-BuNH₂ (0.625 ml, 0.0056 mol), yellow crystalline powder from aqueous MeOH, m.p. 181-83°, yield 72-77%, HPLC purity 98.2 to 99.6%. UV, IR provided in (Table 1), and ¹H NMR in (Table 2).

CIDFB (6a): Red powder, m.p. 230-32°, yield 88-95%, UV, IR (Table 1), ¹H NMR (Table 2), MS (20 ev) *m/z* (rel.int.), 416 (M⁺, 25.4), 350 (M⁺-BF₂OH, 100), 281 (3.4), 273 (8.5), 177 ($C_{10}H_9O_3^+$, 62.7), 138 (83), 124 (53.4).

CIII (3) from 4-hydroxybenzaldehyde (2.463 g, 0.02 mol), AADFB (1.48 g, 0.013 mol), n-ButNH₂ (0.180 ml, 0.0016 mol), orange plates from CHCl₃-CH₃CN, m.p. 231-33°, yield 60-65%, HPLC purity 98.5-99.5%, UV, IR (Table 1). CIIIDFB (9): Red powder, m.p. 221-24°, yield 80-90%, UV (Table 1).

Synthesis of CII:

Vanillin (1.531 g, 0.01 mol), 4-hydroxybenzaldehyde (1.231 g, 0.01 mol), AADFB (1.5 g, 0.113 mol) and n-BuNH₂ (0.18 ml, 0.0016 mol) were used to carry out the reaction in EtOAc as described under CI and CIII. Difluoroboronites of CI, CII and CIII were formed (TLC). By the usual workup

TABLE 1: UV AND IR DATA OF COMPOUNDS

Compound	UV λ$_{max}$ nm (log ε)		IR Flat
	MeOH	**MeOH+alkali**	υ $_{max}$ cm⁻¹
13	349 (3.94)	-	2923,1600,1567,1537,804
14	389 (4.08)	-	1590,1538,1491,812
1	430 (4.71)	486 (4.68)	3386,2875,1628,1603,1510,962,836
6a	501 (4.82)	629 (4.78)	3448,2924,1592,1541,1508,975,817
10	462 (4.36)	-	1764,1618,1599,1588,1544,1508,965,846
2	424 (4.68)	470 (4.59)	3423,2922,1625,1602,1585,1511,960,826
8	493	611	-
11	458 (4.32)	-	1762,1624,1599,1545,1507,981,836
3	418 (4.77)	465 (4.69)	3432,1629,1601,1583,1576,1511,976,833
9	486	594	-
12	454 (4.31)	-	1756,1621,1598,1582,1542,1276,978,836

TABLE 2: ¹H NMR DATA OF COMPOUNDS (1), (6A) AND (12) (200 MHZ) PPM FROM TMS AS INTERNAL STANDARD, J (HZ)

H	(1)[a,b]	(6a)[c]	(12)[a]
4,4'	7.59, 2 H, *d* (15.8)	7.89, 2 H, *d* (15.6)	8.03, 2 H, *d* (15.6)
6,6'	7.15, 2 H, *d* (2)	7.41, 2 H, *d* (1.6)	7.20 to 7.25, 4 H, *m*
10,10'	7.08, 2 H, *dd* (1.8, 9)	7.30, 2 H, *dd* (1.9,8.6)	
9,9'	6.93, 2 H, *d* (8.2)	6.91, 2 H, *d* (8)	7.11, 2 H, *d* (8)
3,3'	6.48, 2 H, *d* (15.8)	6.93, 2 H, *d* (14.6)	6.67, 2 H, *d* (15.6)
1	5.81, 1 H, *s*	6.38, 1 H, *s*	6.11, 1 H, *s*
7,7'-2 OMe	3.97, 3.95, 6 H, *s, s*	3.94, 3.87, 6 H,*s,s*	3.90, 6 H, *s*
8,8'-2 OAc	-	-	2.34, 6 H, *s*

[a]CDCl3, [b]data correspond well with those reported[12] in (CD₃)₂CO and [c](CD₃)₂CO

no solid separated. The product was extracted with EtOAc and washed with water, dried (Na$_2$SO$_4$) and evaporated. The resulting solid (3.9 g) contained CII difluoroboronite (CIIDFB) (8) as the major component and appeared as the middle spot in TLC, The mixture of difluoroboronites could not be separated by CC.

The mixture (2 g) was hydrolyzed with aq. MeOH as described under CI and CIII resulting in the formation of CI, CII and CIII (1.77 g). The mixture (1 g) was subjected to CC and eluted with CHCl$_3$ and CHCl$_3$-MeOH mixtures. CHCl$_3$ eluates gave CI. The initial eluates of 1% MeOH in CHCl$_3$ gave a mixture of CI and CII. The later eluates gave pure CII (0.32 g). The 2% MeOH in CHCl$_3$ gave CII and CIII mixture. Roughly and Whiting[12] used preparative TLC for separation of the three components.

CII (2): Orange brown crystalline powder from CHCl$_3$-CH$_3$CN, m.p. 170-72°, yield 32-35%, HPLC purity 97.5-98.5% UV, IR (Table 1).

Preparation of CIDFB from CI:
To the CHCl$_3$ solution of CI (23 mg in 1 ml) BF$_3$.Et$_2$O (0.5 ml) was added and kept in cold for 5 h. It was then poured into cold water, extracted with CHCl$_3$, the extract washed with water, dried (Na$_2$SO$_4$), evaporated and weighed (23.8 mg). The product was identical in all respects with the synthetic product mentioned above (Scheme 1).

Preparation of CIIDFB for UV spectra:
CII (3 mg) was treated with CHCl$_3$ (10 ml) and BF$_3$.Et$_2$O (0.2 ml) and kept at RT for 1 h. CHCl$_3$ was evaporated and the residue washed with water by decantation a few times, dissolved in acetone and evaporated to dryness. The residue was dissolved in MeOH for UV spectral measurement (Table 1).

Preparation of diacetyldifluoroboronites of CI, CII and CIII:
The curcuminoid (50 mg) was dissolved in acetic anhydride (3 ml) and ether (2 ml) and treated with
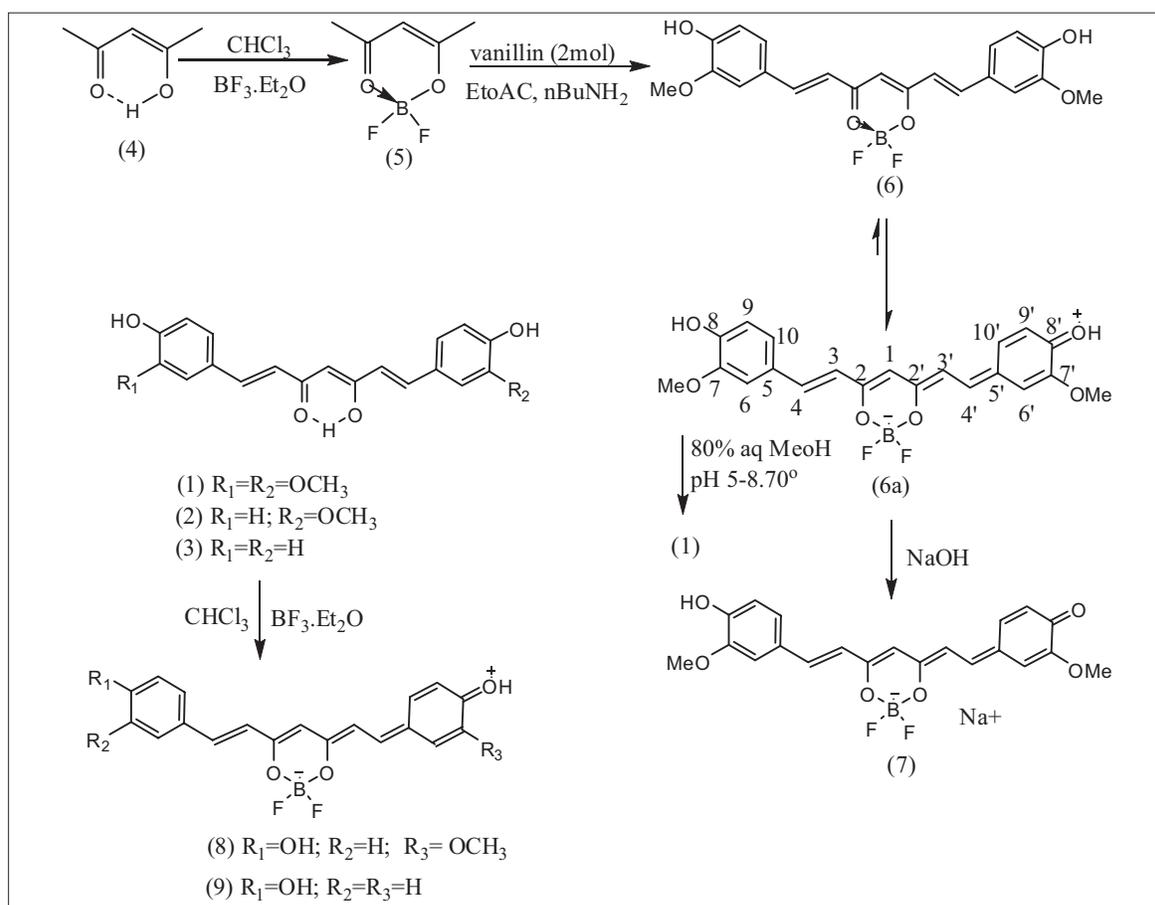
Scheme 1: Synthesis of curcumin and structures of curcuminoids and their difluoroboronites
BF$_3$.Et$_2$O is borontrifluoride etherate, CHCl$_3$ is chloroform, EtOAc is ethyl acetate, n-BuNH$_2$ is n-butylamine, MeOH is methanol and NaOH is sodium hydroxide

BF$_3$.Et$_2$O (1 ml), stoppered and kept in the cold for 24 h. It was then poured into cold water under stirring and kept at RT for 2 h. The light yellow solid that separated was filtered, washed with cold aqueous NaHCO$_3$, followed by water and dried. The product was purified by passing acetone solution through a small column of silica gel and eluting with acetone (Scheme 2).

Diacetyl CIDFB (10) (53.4 mg): m.p. 226-29°, UV, IR (Table 1), ^{1}H NMR (Table 2), MS (20 ev) m/z (rel.int), 500 (M$^+$, 6) 458 (M$^+$-C$_2$H$_2$O, 39), 416 (M$^+$-C$_4$H$_4$O$_2$, 32.2), 350 (M$^+$-C$_4$H$_4$O$_2$-BF$_2$OH,100), 282 (4.2), 238 (7.2), 177 (C$_{10}$H$_9$O$_3$$^+$, 43.2), 124 (4.7). Diacetyl CIIDFB (11) (54.2 mg): m.p. 219-21°, UV, IR (Table 1). Diacetyl CIIIDFB (12) (56.3 mg): m.p. 236-39°, UV, IR (Table 1).

Deacetylation of (10): The substance (10 mg) was treated with NaHCO$_3$ in MeOH (0.8 ml) (prepared by mixing 0.1 ml of saturated aq NaHCO$_3$ with 1 ml of MeOH) and kept at RT for 90 min with occasional shaking. Water (2 ml) was added and extracted with CHCl$_3$. The CHCl$_3$ layer was washed with water, filtered, dried (Na$_2$SO$_4$) and the solvent evaporated. The product was identical with CIDFB obtained by synthesis.

Preparation of Pongamol difluoroboronite (PDFB) (14):
(a) Pongamol[20] (13) (30 mg) was treated with acetic anhydride (1.5 ml) and ether (1 ml) and the solution kept at 0°. BF$_3$.Et$_2$O (0.3 ml) was added drop wise. The flask was stoppered and kept in refrigerator for 5 h. Immediately after the addition of BF$_3$.Et$_2$O, a deep red color appeared which slowly changed to deep yellow with separation of crystals. The crystalline product was filtered, washed with cold aq NaHCO$_3$ and water and dried (Scheme 3). PDFB (14) (23.4 mg): m.p. 215-18°, negative Fe^{+++} reaction and insoluble in 5% aq. NaOH.

(1) R$_1$=R$_2$=OCH$_3$
(2) R$_1$=H; R$_2$=OCH$_3$
(3) R$_1$=R$_2$=H

(10) R$_1$=R$_2$=OCH$_3$;   R$_3$=R$_4$=OCOCH$_3$;
(11) R$_1$=H, R$_2$=OCH$_3$;   R$_3$=R$_4$=OCOCH$_3$;
(12) R$_1$=R$_2$=H;   R$_3$=R$_4$=OCOCH$_3$;

aq MeOH.NaHCO$_3$

(6a), (8), (9)
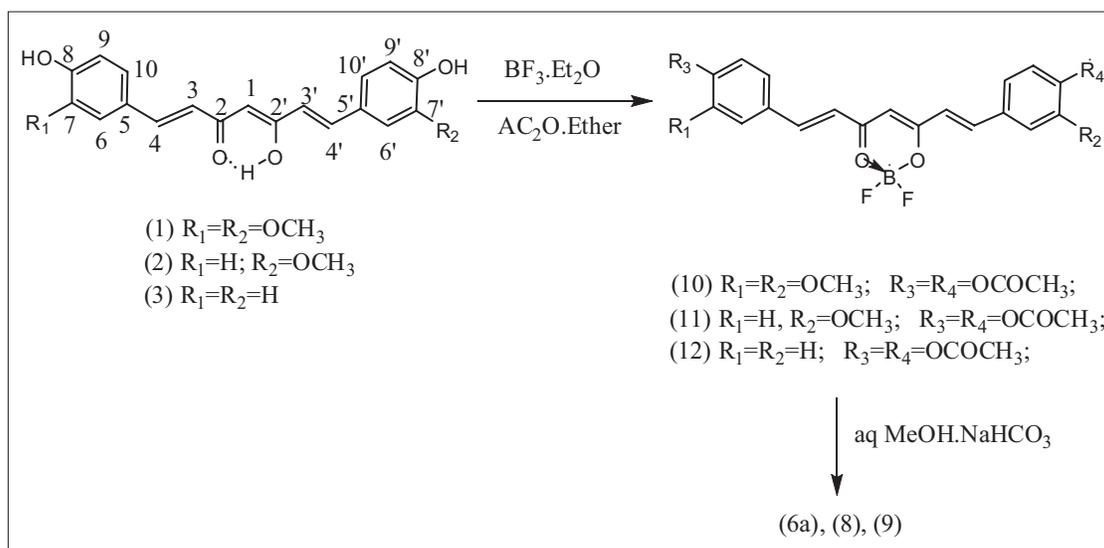
Scheme 2: Preparation of diacetylcurcuminoiddifluoroboronites
BF$_3$.Et$_2$O is borontrifluoride etherate, Ac$_2$O-Et$_2$O is aceticanhydride-diethylether, MeOH is methanol and NaHCO$_3$ is sodiumbicarbonate

(13)

BF$_3$.Et$_2$O in benzene or
Ac$_2$O-ether

MeOH.HCl

(14)
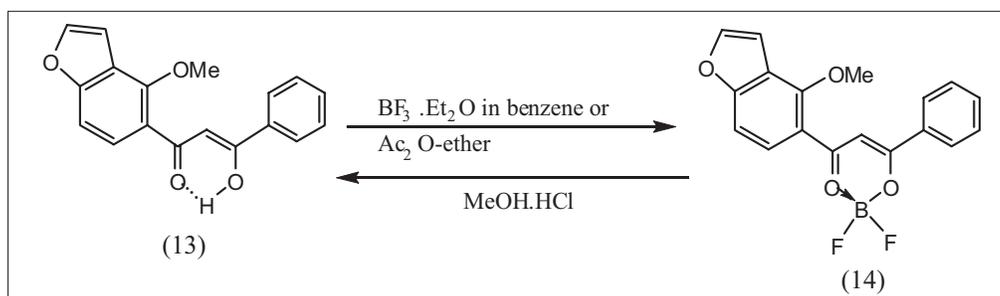
Scheme 3: Preparation of pongamoldifluoroboronite
BF$_3$.Et$_2$O is borontrifluoride etherate, Ac$_2$O-Et$_2$O is aceticanhydride-diethylether, MeOH is methanol
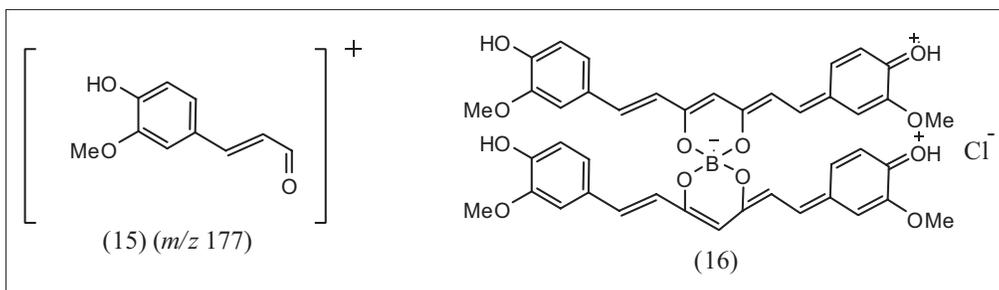
Fig. 1: Structures of curcumin mass fragment (15) and rosocyanin (16)

(b) Pongamol (10 mg) was treated with benzene (3 ml) and $BF_3.Et_2O$ (0.2 ml) and kept at 60° for 3 h. Benzene was evaporated and to the residue MeOH was added drop wise when a yellow crystalline solid separated (7.6 mg), m.p. 216-218° identical with the product under (a), UV, IR (Table 1). PDFB moved slower than pongamol in TLC (viewed in ordinary light and UV chamber)

Hydrolysis of (14):
The substance (10 mg) was treated with MeOH (2 ml) and 1 drop of 6N HCl and heated under reflux at 70° for 3 h. Cold water (10 ml) was added to the reaction mixture and extracted with $CHCl_3$. The $CHCl_3$ layer was washed free from acid with water, dried (Na_2SO_4) and evaporated to get a crystalline solid (8.2 mg), identical with pongamol in all respects.

RESULTS AND DISCUSSION

That CIDFB (6) or (6a) was an intermediate in the synthesis of CI (1) (Scheme 1), also obtained directly from CI by reaction with $BF_3.Et_2O$, is evident from its negative ferric reaction and lower mobility in TLC with the spot turning blue on exposure to ammonia vapor while CI turns orange. In the MS of CIDFB the M^+ was observed at m/z 416 consistent with the formula $C_{21}H_{19}O_6BF_2$ with the base peak at 350 (M^+-66) and the characteristic CI fragment[21] (15) at m/z 177. The MS of the diacetyl derivative (10) was similar with M^+ at m/z 500, consistent with the formula $C_{25}H_{23}O_8BF_2$. However the prior loss of acetyl groups precedes the formation of the base peak at m/z 350 and the CI fragment at m/z 177 (fig. 1)

In accordance with the reported structures of difluoroboronites of β-diketones[17], CIDFB will be expected to have structure (6). While PDFB structure (14) conforms to this view, CIDFB does not as per the UV and IR spectral data (Table 1). In pongamol (13) the IR band at 1600 cm^{-1} represents both the chelated carbonyl and the –C=C– group. In the corresponding difluoroboronite (14), the –C=C– band got shifted to 1538 cm^{-1} with greater intensity and the chelated carbonyl appeared at 1590 cm^{-1}. In acetylacetone (4) and its difluoroboronite (5), the shift in IR of –C=C– band is 63 cm^{-1} (from 1622 to 1559 cm^{-1}) as observed by us. In CI (1) the chelated carbonyl and –C=C– bands appear at 1628 and 1603 cm^{-1} respectively. While the –C=C– band of CIDFB appears at 1541 cm^{-1}, the chelated carbonyl band is absent. However in the diacetyl CIDFB (10), the –C=C– band appeared at 1544 cm^{-1} and the chelated carbonyl band at 1618 cm^{-1} (Table 1). This shows that CIDFB structure differs from that of CI and diacetyl CIDFB. This is also evident from the UV spectra.

The UV data (Table 1) shows that the λ_{max} of PDFB (14) exhibits a bathochromic shift of 40 nm from that of pongamol (13). A similar difference (32 nm) was observed for CI (1) and diacetyl CIDFB (10), whereas the difference in λ_{max} of CI and CIDFB is large (71 nm). This suggests a difference in the structure pattern with additional conjugation in CIDFB. This was also the case with CII (2), CIII (3) and their corresponding difluoroboronites (8) and (9) and their diacetyl difluoroboronites (11) and (12). Based on these facts, the structure for CIDFB is more in favour of the quinonoid form (6a) than (6). This is further indicated by the observation that the red color of CIDFB in MeOH with λ_{max} 501 nm acquires a deep blue color on the addition of alkali with λ_{max} 629 nm. CI itself shows a bathochromic shift of 56 nm on the addition of alkali. However, the shift is far greater (128 nm) on the addition of alkali to CIDFB. The deep blue colored product (in solution, pH 11.7) is tentatively assigned the structure (7). Similar was the case with CII and CIII and their corresponding difluoroboronites.
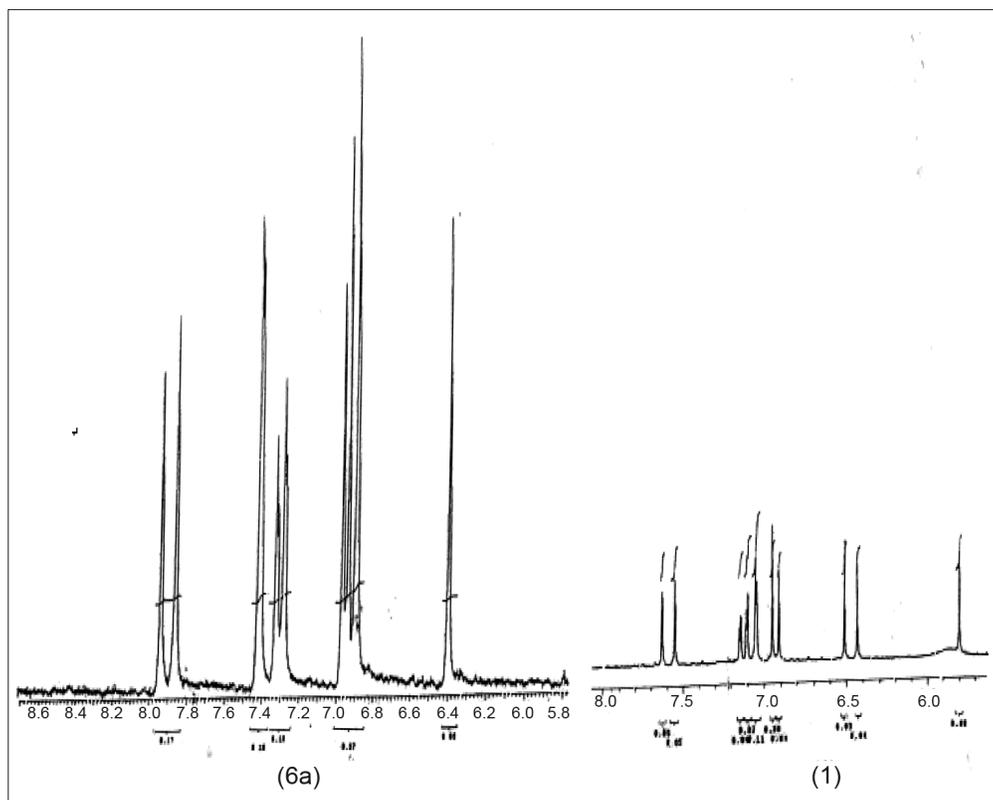
Fig. 2: Enlarged ¹H NMR spectrum of compounds (6a) and (1) in the region 5.5-8.6 ppm
¹H NMR is proton magnetic resonance
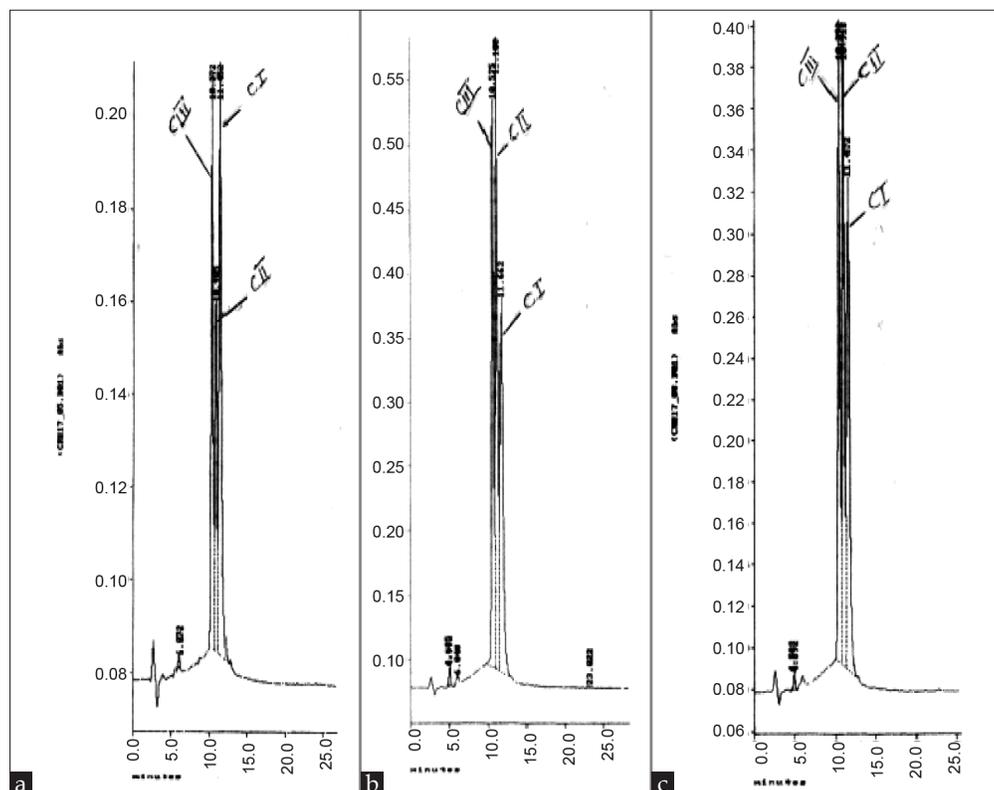
Fig. 3: HPLC chromatogram of natural, synthetic and natural+synthetic curcuminoids
t_R for a, natural curcuminoids: 10.37 (C III), 10.90 (C II) and 11.45 min (C I), t_R for b synthetic curcuminoids: 10.57 (C III), 11.11 (C II) and 11.66 min (C I) and t_R for c natural + synthetic: 10.39 (C III), 10.92 (C II) and 11.47 min (C I)

The ^{1}H NMR spectral data of CI and its derivatives (Table 2) also seem to confirm the structure assigned to CIDFB (6a) and its diacetyl derivative (10). The data show downfield shift of all protons (other than methoxyls) in (6a) and (10). The 6,6' and 10,10' protons in (10) appear as a multiplet as in diacetyl CI[12]. The ^{1}H NMR of (6a) differs from that of (1) and (10) in respect of 3,3' and 9,9' proton peaks. These four protons appear like three singlets accounting for 1+1+2 protons. We consider them as double doublets (*dd*) with the peak at 6.89 ppm integrating for two protons being common for both the doublets (fig. 2) and represent both 3' and 9' protons. Also the splitting of methoxyl protons in (6a) is significantly more than in (1).

Rosocyanin (fig. 1), the compound formed when two molecules of CI (1) react with boric acid in the presence of mineral acid (concentarted H_2SO_4 or HCl), had been assigned the quinonoid structure[22] (16), supported by IR data[23]. This compound, isolated following a devious procedure[22], was a dark green powder with metallic luster decomposing at *ca.* 250° without melting.

The next important stage in the synthesis is cleavage of the difluoroboronites to generate the diketones. The difluoroboronites of acetylacetone, benzoylacetone and dibenzoylmethane were reported[18] to decompose in moist air or warm alcohol liberating HF and orthoboric acid. PDFB (14) could be hydrolyzed with MeOH containing a little HCl, which hastened the reaction. CIDFB (6a) (as also CIIIDFB) is stable in acid medium and indeed it was isolated at pH 3. The red colored difluoroboronite solution in aq. MeOH showed a pH of 5.63 initially, but an hour after heating at 70° the pH changed to 3 due to release of HF with the solution turning deep red and further hydrolysis slowing down considerably. It was necessary to adjust the pH to *ca.* 5.8 and maintain it for complete hydrolysis. At pH 7 and above a deep blue solution is obtained resulting in intractable products. The 4/4' free OH in the aryl groups is necessary for quinonoid formation. Dimethyl CIDFB underwent cleavage with relative ease and did not give blue colour with alkali. The synthetic curcuminoids obtained by our method are identical with the natural samples in all respects including HPLC. The HPLC chromatograms of natural, synthetic and mixed natural and synthetic curcuminoids are presented in fig. 3.

Our studies show that borontrifluoride is an effective and less costly reagent than boric oxide to protect the enol group in acetyl acetone. The use of expensive trialkylborate can be dispensed with. The intermediate difluoroboronites are stable and can be cleaved whenever required. The synthetic strategy will enable the preparation of a variety of curcuminoids in pure state and good yield for appropriate biological activity and clinical studies.

ACKNOWLEDGEMENTS

REFERENCES

1. Chattopadhyay I, Biswas K, Bandyopadhyay U, Banerjee, RK. Turmeric and curcumin: Biological activity and medicinal applications. Curr Sci (India) 2004;87:44-53.
2. Kulkarni SK, Dhir A. An overview of curcumin in neurological disorders. Indian J Pharm Sci 2010;72:149-54.
3. Satokar RR, Shah SJ, Shenoy SG. Evaluation of anti-inflammatory property of curcumin (deferuloylmethane) in patients with post-operative inflammation. Int J Clin Pharmacol Ther Toxicol 1986;24:651-4.
4. Rao EV. Turmeric and curcumin. Curr Sci (India) 2004;87:1324.
5. Internet News: Turmeric- an effective therapy for Crohn's disease. Natural Product Radiance (CSIR) 2004;3:115.
6. Rovner SL. Untangling Alzheimer's. Chem Eng News 2005;83:38-45.
7. Roth GN, Chandra A, Nair MG. Novel bioactivities of *Curcuma longa* constituents. J Nat Prod 1998;61:542-5.
8. Masuda J, Jitoe A, Isobe J, Nakatani N, Yonemori S. Anti-oxidative and anti-inflammatory curcumin-related phenolics from rhizomes of *Curcuma domestica*. Phytochemistry 1993;32:1557-60.
9. Mazumdar A, Neamati N, Sunder S, Schulz J, Pertz H, Eich E, *et al*. Curcumin analogs with altered potencies against HIV-I integrase as probes for biochemical mechanisms of drug action. J Med Chem 1997;40:3057-63.
10. Erraguntla VR, Paladugu S. An improved process for the preparation of curcumin. Indian Patent 192887; April 21, 2005 (Assignee: Natco Pharma Ltd.)
11. Pabon HJ. A synthesis of curcumin and related compounds. Rec Trav Chim 1964;83:379-86.
12. Roughley PJ, Whiting DA. Experiments in the biosynthesis of curcumin. J Chem Soc Perkin I 1973;2379-88.
13. Graf E. Curcumin from vanillin and acetyl acetone. German. Patent 1,280,849; Oct. 24.1968.
14. Krackov MH, Bellis HE. Process for the synthesis of curcumin related compounds. US Patent 5,679,864; Oct. 21.1997.
15. Babu KV, Rajasekharan KN. A convenient synthesis of curcumin-I and its analogues. Org Prep Proc Int 1994;26:674-7.
16. Bhat MV, Kulkarni SU. Cleavage of ethers (Review). Synthesis 1983;249-82.

17. Lappert MF. Organic compounds of boron. Chem Rev 1956;56:961-1064.
18. Morgan GT, Turnstall RB. Boron β-diketonedifluorides. J Chem Soc 1924;125:1963-7.
19. Narayanaswamy S, Rangaswami S, Seshadri TR. Chemistry of pongamol part II. J Chem Soc 1954;1871-3.
20. Pelter A, Ward RS, Rao EV, Raju NR. 8-Substituted flavonoids and 3'-substituted-7-oxygenated chalcones from *Tephrosia purpurea*. J Chem Soc Perkin I 1981;2491-8.
21. Matthes HW, Luu B, Ourisson G. Cytotoxic components of *Zingiber zerumbet*, *Curcuma zeodaria* and *C. domestica*. Phytochemistry 1980;19:2643-50.
22. Spicer GS, Strickland JD. Compounds of curcumin and boric acid, part I, the structure of rosocyanin. J Chem Soc 1952;4644-50.
23. Bellamy LJ, Spicer GS, Strickland JD. Compounds of curcumin and boric acid, part III, infra-red studies of rosocyanin and allied compounds. J Chem Soc 1952;4653-6.